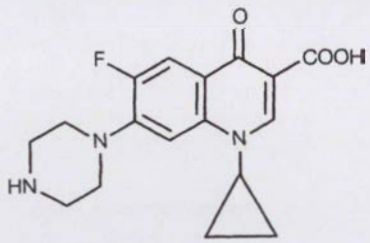
PRODUCT INFORMATION

CIPROXIN™ IV (Ciprofloxacin; ~~Bayer~~)

~~FOR INTRAVENOUS INFUSION~~

NAME OF THE MEDICINE

Ciproxin™ IV (Ciprofloxacin) is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity for intravenous (IV) administration. Ciprofloxacin, a fluoroquinolone, is a 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. The CAS Registry number is 85721-33-1. It is a faint to light yellow crystalline powder with a molecular weight of 331.4. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is as follows:



DESCRIPTION

Ciproxin IV (Ciprofloxacin lactate) is available as a 100 mg/50 mL and a 200 mg/100 mL ready-to-use infusion solution in 0.9% sodium chloride injection. CIPROXIN IV also contains the excipients: lactic acid, which is used as a solubilizing agent, hydrochloric acid for pH adjustment, and water for injections. The solution is a clear, colourless to slightly yellow solution.

~~CLINICAL~~ PHARMACOLOGY

Pharmacokinetics

Distribution

Immediately following a 30-minute intravenous infusion of 200 mg ciprofloxacin, serum concentrations average 3 mcg/mL. During the first hour after completion of infusion, serum concentration decreases to approximately 30% of the peak value, but thereafter serum concentrations decline with a half-life of approximately 4 hours. Mean concentrations observed after a 200 mg dose are given below:

Ciprofloxacin Serum Concentrations (mcg/mL)
After a 30-minute Infusion

Dose	End of Infusion	0.5 hr	1 hr	3 hr	6 hr	8 hr	12 hr
200 mg	3.18	1.4	1.0	0.5	0.3	0.2	0.1

The pharmacokinetics of intravenously administered ciprofloxacin are near-linear over the dosage range of 100 mg to 300 mg, as no substantial dose-dependent changes in clearance or serum half-life are observed.

As per ARGPM format

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As per ARGPM format Format change to headings

Approximately 50-70% of the intravenous dose is excreted in the urine as unchanged drug. During the first 2 hours of a 200 mg intravenous dose, the urine concentration of ciprofloxacin usually exceeds 200 mcg/mL.

As per ARGPM format
Format change to headings

Metabolism

Four metabolites, desethyleneciprofloxacin (M_1), sulphociprofloxacin (M_2), oxociprofloxacin (M_3) and formylciprofloxacin (M_4), have been identified in human urine which, together, account for approximately 12% of an intravenous dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Excretion

Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/hr which exceeds the normal glomerular filtration rate of 7.2 L/hr. Thus, active tubular secretion would seem to play a significant role in its elimination.

Although bile concentrations of ciprofloxacin are 3-4 times higher than serum concentrations after intravenous dosing, only a small amount of the dose administered (<1%) is recovered from bile as unchanged drug.

An additional 1-2% of the dose is recovered from bile in the form of metabolites.

Approximately 15% of an intravenous dose is recovered from the faeces within 5 days after dosing.

Protein Binding

Binding of ciprofloxacin to serum protein is 20-40%.

Factors influencing pharmacokinetics

Impaired renal/hepatic function

In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is slightly prolonged, but dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half-life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see Dosage and Administration). Serum metabolite concentrations, particularly sulfociprofloxacin (M_2) and oxociprofloxacin (M_3), are higher in renally impaired patients than in patients with normal renal function.

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics were observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Age (elderly)

The higher levels of ciprofloxacin and its metabolites seen in elderly patients are possibly due to reduced renal function and volume of distribution.

~~PHARMACOLOGY (~~Inhalational anthrax~~)~~

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens. (See DOSAGE AND ADMINISTRATION). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12

hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 µg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

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~~MICROBIOLOGY~~ Pharmacological actions

Ciprofloxacin has *in vitro* and *in vivo* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase.

Gram-negative organisms

Escherichia coli; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species (including *Serratia marcescens*); *Pseudomonas aeruginosa*; *Pseudomonas fluorescens*; *Haemophilus influenzae*; ~~*Neisseria gonorrhoeae*~~; *Moraxella* (*Branhamella*) *catarrhalis*; *Campylobacter* species.

As per CCDS update to "varying degrees of sensitivity"

Gram-positive organisms*

Staphylococcus aureus (including methicillin susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes* (group A); *Streptococcus pneumoniae*; *Enterococcus faecalis*.

See overleaf

Note: *

1. Gram-positive organisms and *Pseudomonas aeruginosa* are generally less sensitive to ciprofloxacin than other Gram-negative organisms which results in lower drug efficacy rates.

2. Most strains of streptococci are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Ciprofloxacin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

4. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

5. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

6. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

7. *Neisseria gonorrhoeae* shows varying degrees of sensitivity

Text moved from "Indications"

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

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Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker.

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2-8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice, resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents. The combination behaves either in an indifferent or additive manner. Synergism or antagonism has been observed very rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Text moved from "indications"

Susceptibility Tests

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to antimicrobial agents. Interpretation involves correlation of the zone diameters obtained by the disc test with minimal inhibitory concentration (MIC) values for ciprofloxacin.

When the causative organism is tested by the modified Kirby-Bauer disc method, susceptibility tests using a 5-mcg ciprofloxacin disc should be interpreted according to the following criteria:

Susceptible organisms produce zone sizes of 21 mm or greater. Zone sizes of 16-20 mm indicate intermediate susceptibility. Zone sizes of 15 mm or less indicate resistance. The ciprofloxacin disc should be used to test susceptibility to ciprofloxacin but it should not be used for testing susceptibility to other quinolones. Standardised procedures require the use of laboratory control organisms.

The quality control limits for the 5-mcg ciprofloxacin disc are the following:

Staphylococcus aureus ATCC 25923, 22-30 mm
Escherichia coli ATCC 25922, 30-40 mm
Pseudomonas aeruginosa ATCC 27853, 25-33 mm

***Dilution Techniques*:** In certain conditions, it may be desirable to determine the susceptibility of rapidly growing aerobic organisms by broth or agar dilution methods. A bacterial isolate may be considered susceptible if the MIC value for ciprofloxacin is not greater than 1 mcg/mL. Organisms are considered resistant if the MIC is greater than 2 mcg/mL. Organisms with MICs greater than 1, but less than 2 mcg/mL are considered as having intermediate susceptibility.

As with standard disc diffusion methods, dilution procedures require the use of laboratory control organisms.

The quality control limits for MIC values are the following:

Staphylococcus aureus ATCC 29213, 0.25-1.0 mcg/mL
Escherichia coli ATCC 25922, 0.008-0.03 mcg/mL
Pseudomonas aeruginosa ATCC 27853, 0.25-1.0 mcg/mL

INDICATIONS

1. Ciprofloxacin IV is indicated for use in hospitalised adult patients in whom oral ciprofloxacin is indicated but cannot be administered or where the oral form is inappropriate.

2. For the treatment of serious or life-threatening infections due to sensitive organisms involving the following organ systems:

   Lower respiratory tract infections (Gram-negative organisms)
   Skin and Skin Structure
   Septicaemia
   Bone and Joint
   Urinary Tract

   NOTE: cipro is not a drug of 1st choice in the treatment of pneumococcal or confirmed pneumonia se---

3. Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

~~Note:~~

~~Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections due to *Streptococcus pneumoniae*.~~

~~If anaerobic organisms are suspected of contributing to the infection, use of other suitable drugs should be considered.~~

Refer CCDS & US PI - deletion is unacceptable - Pharmacy to report

Text deleted (captured in note #2 and note #3 under "Ph. Actions")

~~Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.~~

~~Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.~~

~~Ciprofloxacin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.~~

Moved to "Pharmacological actions" as per CCDS wording

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CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or other quinolones (including nalidixic acid), or any of the excipients is a contraindication to its use.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine-induced side effects (hypotension, somnolence, drowsiness) can occur.

~~WARNINGS~~ PRECAUTIONS

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The use of ciprofloxacin in pre-pubertal children – except for use in inhalational anthrax (post-exposure) – and during pregnancy is not recommended (see Precautions).

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with CIPROXIN (ciprofloxacin) and other quinolones. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Therapy should be discontinued if the patient experiences pain, inflammation or rupture of a tendon.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Increased toxicity of intravenous ciprofloxacin has been associated with increased duration of use, hence oral ciprofloxacin should be substituted as soon as practicable.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). Some reactions are accompanied by cardiovascular collapse. Appropriate emergency measures for the management of such reactions should be readily available.

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

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~~PRECAUTIONS~~

General

Ciprofloxacin intravenous solution should be administered by slow infusion over a period of 60 minutes. Local IV site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 60 minutes or less or if small veins of the hand are used. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9.

Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

The additional sodium load should be taken into account when using Ciproxin IV in patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) See "PRESENTATION" or "ADMINSTRATION" for sodium content.

CNS Effects

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

Cytochrome P450:

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. theophylline, methylxantines, caffeine, duloxetine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also Interaction With Other ~~DRUGS~~ Medicines)

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Epileptic Patients

Ciprofloxacin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects.

Nervous System

Ciprofloxacin might exacerbate symptoms of myasthenia gravis. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Format change to headings

Elderly Patients

Ciprofloxacin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see Dosage and Administration).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and haematopoietic, is advisable during prolonged therapy.

Effects on The Liver

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

~~DRUG INTERACTIONS~~ Interactions with Other Medicines

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Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline, prolongation of its elimination half-life and increased adverse reactions, particularly those involving the CNS.

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN IV AND THEOPHYLLINE. These reactions include cardiac arrest, convulsive seizures, status epilepticus and respiratory failure. Similar serious adverse events have been noted with administration of theophylline alone; however, the possibility that ciprofloxacin may potentiate these reactions cannot be eliminated. **If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.**

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Caffeine

Quinolones have also been shown to interfere with the metabolism of caffeine. It may reduce the clearance of caffeine and prolong its plasma half-life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Probenecid

Probenecid interferes with the renal excretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance, a 50% increase in AUC but without altering peak concentration or time to peak.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly.

Glibenclamide

In particular cases, concurrent administration of ciprofloxacin and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin. (see also **CONTRAINDICATONS**)

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Use in Pregnancy

Pregnancy Category B3

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Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastro-intestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals. Ciprofloxacin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

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Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid, norfloxacin and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION.** The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

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Mutagenicity ~~AND CARCINOGENICITY~~

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay *in vitro*, but not in other mammalian systems *in vitro* or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

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Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

ADVERSE ~~REACTIONS~~ EFFECTS

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~~profloxacin IV was generally well tolerated in the reported clinical trials at the recommended doses. Adverse events that were considered likely to be drug-related occurred in 7.1% of courses, possibly related in 8.6%, and remotely related in 3.4%. The overall incidence of adverse reactions (29%) was higher than after oral ciprofloxacin (19%). Incidence increased progressively with increase in duration of treatment beyond 7 days.~~

~~The most frequently reported events, drug-related or not, were nausea, diarrhoea, vomiting, rash, CNS disturbances, injection site reactions *(e.g. oedema, hypersensitivity, inflammation, pain), abnormalities of liver enzymes and eosinophilia.~~

~~Additional events, drug-related or not, that occurred in 1% or less of ciprofloxacin courses are listed below:~~

~~**Gastrointestinal** - mouth dryness, oral candidiasis, plaque on dentures, painful oral mucosa, dysphagia, anorexia, flatulence, constipation, vomiting, dyspepsia, epigastric pain, gastric irritation, ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhoea, life threatening pseudomembranous colitis with possible fatal outcome, pancreatitis, hepatic necrosis, intestinal perforation.~~

~~**Hepatic** - allergic hepatitis, cholestatic jaundice, very rarely major liver disorders including hepatic necrosis.~~

~~**CNS** - hallucinations, confusion, convulsive seizures, nightmares, tremor, psychotic reaction (even progressing to self-endangering behaviour), depression, lethargy, drowsiness, somnolence, anxiety, nervousness, headache, dizziness, weakness, paraesthesia, dysphasia, manic reaction, sweating, unsteady gait, paranoia, ataxia, irritability, depersonalisation, insomnia, increase in intracranial pressure, peripheral paralgesia, hypaesthesia, hyperaesthesia, hypertonia, twitching.~~

~~**Skin/hypersensitivity** - erythema, burning, increased perspiration, urticaria, fever, photosensitivity reactions, angioedema, flushing, pruritus, chills, cutaneous candidiasis, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, hyperpigmentation, erythema nodosum, erythema multiforme exudativum (minor), papules, petechiae, Lyell syndrome, haemorrhagic bullae, serum-sickness like reaction, fixed eruption.~~

~~Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic, produces photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.~~

~~**Body as a whole** - fatigue, malaise, aches, hot flushes, pain, pain in extremities, back pain, chest pain, *injection site reaction, (e.g.oedema/hypersensitivity/inflammation/pain)~~

~~**Special senses** - disturbed vision (blurred vision, colour vision, flashing lights, overbrightness of lights, diplopia), decreased visual acuity, retro-ocular pain, transient impairment of hearing especially at high frequencies, tinnitus, bad taste, impaired smell, loss of smell (usually reversible on discontinuation).~~

~~**Respiratory** - epistaxis, laryngeal oedema, wheezing, dyspnoea, hiccough, coughing, pulmonary embolism, respiratory arrest, respiratory distress, pleural effusion.~~

~~**Metabolic or Renal** - interstitial nephritis, nephritis, renal failure, flare-up of gout, acidosis, hyperglycaemia.~~

Urogenital - crystalluria, dysuria, polyuria, candiduria, vaginitis, haemorrhagic cystitis, urethral bleeding.

Cardiovascular - cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, cerebral thrombosis, palpitations, cardiac murmur, hypertension, hot flushes, migraine, syncope, hypotension, angina pectoris, *(thrombo-) phlebitis (at infusion site). # 0.1-1% - frequency - (missing).

Musculoskeletal - muscular pain, myasthenia, joint pain, joint swelling, tenosynovitis, tendovaginitis, tendinitis, predominantly affecting the achilles tendon, exacerbation of symptoms of myasthenia gravis. Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Patients who are elderly or have had prior systemic treatment with corticosteriods are thought to be at particular risk. Therapy should be discontinued if the patient experiences pain, inflammation or rupture of a tendon.

Intravenous infusion site - burning, pain, erythema, swelling, paraesthesia, pruritus. Thrombophlebitis accounted for half the local reaction at the site of intravenous infusion, with the remainder being erythema, pruritus or burning pain. These reactions are more frequent with infusion time of 60 minutes or less.

Most of these events which were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances nausea, vomiting, tremor, restlessness, agitation or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Also reported were agranulocytosis, prolongation of prothrombin time and possible exacerbation of myasthenia gravis.

Adverse Laboratory Changes

Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic	- Elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, serum bilirubin.
Renal	- Elevations of serum creatinine, serum urea, uric acid.
Urinalysis	- Crystalluria, haematuria and albuminuria have been reported.
Haematologic	- Eosinophilia, decreased blood platelets (thrombocytopenia), elevated blood platelets (thrombocytosis), decreased haemoglobin/ haematocrit, leukopenia, leukocytopenia, granulocytopenia.
Other	- Elevations of serum creatinine, phosphokinase, elevations of serum theophylline (in patients receiving theophylline concomitantly), blood glucose, triglycerides.

Document 1

~~Changes occurring in 0.1% or less of courses were:~~

~~ecreased serum urea, elevated serum potassium, decreased serum potassium, decreased uric acid, elevated serum calcium, decreased total serum protein, elevated atypical lymphocyte count, decreased lymphocyte count, elevation of serum gamma-glutamyl transpeptidase (γ-GT), decrease in platelet count, increase in blood monocytes, hyperglycaemia, immature WBCs, decreased serum albumin, cylindruria, elevated serum cholesterol.~~

~~Other changes occurring rarely during the administration of ciprofloxacin were elevation of serum amylase, lipase increased, decrease in blood glucose, pancytopenia (life-threatening), marrow depression (life-threatening), leukocytosis, elevated sedimentation rate, elevation of serum phenytoin (in patients receiving phenytoin concomitantly), decreased prothrombin time, haemolytic anaemia and bleeding diathesis.~~

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

ADRs derived from post marketing reports (status: 31 July 2005) are printed in *italic*.

Common ≥1% to <10%	**Uncommon** ≥0.1% to < 1%	**Rare** ≥0.01% to <0.1%	**Very rare** <0.01%
Infections and Infestations			
	Candida infections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia *(life-threatening)* Bone marrow depression *(life-threatening)*
Immune System Disorders			
		Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock *(life-threatening)* *Serum sickness-like reaction*
Metabolism and Nutrition Disorders			
	Anorexia	Hyperglycemia	
Psychiatric Disorders			
	Psychomotor hyper-activity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions

Hypocalaemia

Common 1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures Vertigo	Migraine Disturbed coordination Smell disorders *Hyperesthesia* *Intracranial hypertension*
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
	Phlebitis.	Vasodilatation Hypotension Syncope	Vasculitis r/thrombophlebitis.
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Transient increase in transaminases Increased bilirubin	Transient hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis *(very rarely progressing to life-threatening hepatic failure)*
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Unspecific blistering	Petechiae Erythema multiforme minor *Erythema nodosum* *Stevens-Johnson syndrome* *Toxic epidermal necrolysis*
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia	Muscular weakness

Common 1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
		Arthritis Increased muscle tone and cramping	Tendonitis Tendon rupture (predominantly Achilles tendon) *Exacerbation of symptoms of myasthenia gravis*
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever , phlebitis. local.	Oedema Sweating (hyper-hidrosis)	*Gait disturbance*
Investigations			
	Transient increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase	

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Intravenous therapy, for the indications mentioned below, should be used only when oral therapy is contraindicated. The usual dosage for adults is 200-300 mg every 12 hours. For complicated infections or for those caused by organisms not highly susceptible, 300 mg should be administered every 12 hours.

DOSAGE GUIDELINES

Location of Infection	Type or Severity	Unit Dose	Daily Frequency	Total Daily Dose
Urinary tract	Severe/ Complicated	200 mg	q 12 h	400 mg

Location of Infection	Type or Severity	Unit Dose	Daily Frequency	Total Daily Dose
Lower respiratory tract infections (gram-negative) Skin or Skin Structure Blood Bone or Joint	Moderate	200 mg	q 12 h	400 mg
	Severe/ Complicated (less susceptible organisms)	300 mg	q 12 h	600 mg

Location of Infection	Type or Severity	Unit Dose	Daily Frequency	Total Daily Dose
Inhalational Anthrax (post-exposure)*	Adult	400 mg	q 12 h	800 mg
	Paediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q 12 h	Not to exceed 800 mg

Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

Ciprofloxacin IV should be administered only by intravenous infusion over a period of 60 minutes. Slow infusion of a dilute solution into a large vein will minimise patient discomfort and reduce the risk of venous irritation.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

The serum creatinine should represent a steady state of renal function.

Duration

The duration of treatment depends upon the severity of infection. Generally, ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days (parenteral therapy should be changed to oral ciprofloxacin tablets as soon as the condition warrants). In general, intravenous ciprofloxacin should not normally be given for greater than 14 days. However, for severe and complicated infections more prolonged therapy may be required. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

For creatinine clearance equal to or less than 30 mL/min/1.73m^2, the maximum daily dose should be 400 mg/day for IV regimen.

When only data for serum creatinine are available, the following formula (Cockroft's equation) may be used to estimate creatinine clearance.

Men:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} \text{ x } 0.0885$$

Women: 0.85 x the above value calculated for men.

Administration

Ciprofloxacin IV infusion solutions (0.2%) are available as a pre-mixed solution in 0.9% sodium chloride, equivalent to approximately 154 mmoL sodium per litre, packed in 50 mL or 100 mL glass bottles.

The solution should be infused over a period of not less than 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the intravenous infusion of ciprofloxacin.

Osmolality of the infusion solution: 300 mOsm/Kg.
Sodium chloride content: 900 mg/100 mL.

If ciprofloxacin IV is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Compatibility and Stability

Ciprofloxacin solutions are incompatible with all infusion solutions/drugs (e.g., penicillins, heparin solutions), which are physically or chemically unstable at the pH of ciprofloxacin (pH 3.9 - 4.5), especially when combined with alkaline solutions.

Since ciprofloxacin is slightly light sensitive, the solutions should be protected from light during storage.

OVERDOSAGE

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The patient should be carefully observed and given appropriate supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after haemodialysis or peritoneal dialysis.

Change to heading as per ARGPM format

PRESENTATION AND STORAGE CONDITIONS

CIPROXIN IV (ciprofloxacin) is a clear, colourless to slightly yellowish solution.
CIPROXIN IV infusion solutions (0.2%) are available in vials containing pre-mixed solutions of ciprofloxacin 100 mg/50 mL and 200 mg/100 mL in 0.9% sodium chloride.

Approved text added as per Cat 3 AN 2006-1052-2

~~STORAGE~~
Store below 30°C. Protect from light. ~~Protect from freezing~~. Do not refrigerate.

Document 1

Instructions for handling

. cool temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
~~Pharmaceutical Business Group~~
875 Pacific Highway
PYMBLE NSW 2073

~~*Please note change(s) in Product Information~~

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF TGA APPROVAL: ~~23 October 2002~~

~~**DATE OF LATEST AMENDMENT:** 15 June 2006~~

™ = Trade Mark of Bayer HealthCare AG, Germany

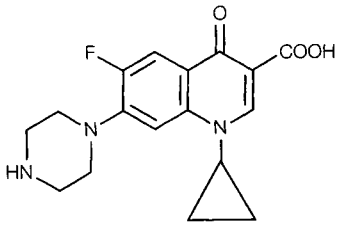
Change to headings as per ARGPM format

PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl \bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGY

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg•hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the

urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION**).

After oral dosing ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens. (See DOSAGE AND ADMINISTRATION.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 μg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 μg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 μg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 μg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared

to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

Pharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

Escherichia coli; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see PHARMACOLOGY).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the

pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients is a contraindication to its use.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine-induced side effects (hypotension, somnolence, drowsiness) can occur.

PRECAUTIONS

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see ADVERSE EFFECTS). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g. known QT prolongation, uncorrected hypokalemia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on Tendons

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any sign of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Pseudomonas aeruginosa Infections in Cystic Fibrosis

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Effects on the CNS

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures. Ciproxin should be used with caution in patients with CNS disorders, such as severe cerebral arteriosclerosis or epilepsy.

In some instances, the CNS reactions occurred after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, Ciproxin has to be discontinued and the physician should be informed immediately.

Nervous System

Ciprofloxacin might exacerbate symptoms of myasthenia gravis. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. theophylline, methylxantines, caffeine, duloxetine, clozapine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also Interaction With Other Medicines)

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Interactions with Other Medicines

Class IA or III antiarrhythmics

Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics as ciprofloxacin may have an additive effect on the QT interval.

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half life of elimination.

Caffeine

Quinolones have also been shown to interfere with the metabolism of caffeine. It may reduce the clearance of caffeine and prolong its plasma half-life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Glibenclamide

In particular cases, concurrent administration of ciprofloxacin and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions, Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Other

Iron, sucralfate or highly buffered drugs (e.g. antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin; concurrent administration of these agents with Ciproxin should be avoided.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be

monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

Epileptic Patients

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Effects on the Liver

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively)

and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay *in vitro*, but not in other mammalian systems *in vitro* or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in

males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium* spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopaenia Anaemia Neutropaenia Leukocytosis Thrombocytopaenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopaenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Anorexia	Hyperglycemia	
Psychiatric Disorders			
	Psychomotor hyper-activity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Unspecific blistering	Petechiae Erythema multiforme minor Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion	Unspecific pain	Oedema	Gait disturbance

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
site reactions (only intravenous administration)	Feeling unwell Fever	Sweating (hyper-hidrosis)	
Investigations			
	Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase	

Note: The incidence of arthropathy, mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopaenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have

disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg- or Ca-containing antacids which reduce the absorption of ciprofloxacin.

Only a small amount of ciprofloxacin (<10%) is removed from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and "250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF APPROVAL

Date of TGA Approval: 18 January 2007

Date of most recent amendment: 16 June 2010

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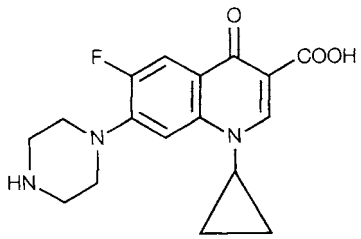
PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl \bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGYPharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

Escherichia coli; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **PHARMACOLOGY**).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg.hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens. (See **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 μg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 μg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to

1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.

- Concurrent administration of ciprofloxacin and tizanidine (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics,) or in patients with risk factors for torsade de pointes (e.g. congenital long QTsyndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on the Liver

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE EFFECTS**). There can be temporary increase in transaminases, alkaline

phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Effects on Tendons

Tendonitis and tendon ruptures (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any sign of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Pseudomonas aeruginosa Infections in Cystic Fibrosis

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Effects on the CNS

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychotic reactions can

progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide.. In the event that the patient develops any of these reactions, Ciproxin should be discontinued and appropriate measures instituted.

Nervous System

Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Patients under treatment with Ciproxin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness or weakness develop (see **ADVERSE EFFECTS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **INTERACTIONS WITH OTHER MEDICINES)**

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin in vitro potency may interfere with the Mycobacterium spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Caffeine

Quinolones have also been shown to interfere with the metabolism of caffeine. It may reduce the clearance of caffeine and prolong its plasma half-life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Other

Iron, sucralfate or highly buffered drugs (e.g. antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin; concurrent administration of these agents with Ciproxin should be avoided.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy, mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and "250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON THE ARTG: 2 March 1992

DATE OF MOST RECENT AMENDMENT: 29 May 2012

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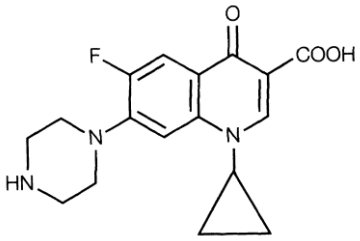
PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl \bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGY

Pharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

> *Escherichia coli*; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **PHARMACOLOGY**).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg•hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute

intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.

- Concurrent administration of ciprofloxacin and tizanidine (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics,) or in patients with risk factors for torsade de pointes (e.g. congenital long QTsyndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile*

should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on the Liver

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE EFFECTS**). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Effects on Tendons

Tendonitis and tendon ruptures (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any sign of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

***Pseudomonas aeruginosa* Infections in Cystic Fibrosis**

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Effects on the CNS

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide. In the event that the patient develops any of these reactions, Ciproxin should be discontinued and appropriate measures instituted.

Nervous System

Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciproxin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **ADVERSE EFFECTS**).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **ADVERSE EFFECTS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **INTERACTIONS WITH OTHER MEDICINES)**

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well

hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of

weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin in vitro potency may interfere with the Mycobacterium spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Caffeine

Quinolones have also been shown to interfere with the metabolism of caffeine. It may reduce the clearance of caffeine and prolong its plasma half-life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Other

Iron, sucralfate or highly buffered drugs (e.g. antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin; concurrent administration of these agents with Ciproxin should be avoided.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and

C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
			(potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy, mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema

Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and “250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD

ABN 22 000 138 714

875 Pacific Highway

PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON THE ARTG

2 March 1992

DATE OF MOST RECENT AMENDMENT

30 July 2015

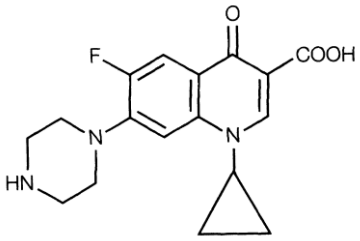
® Registered Trade Mark of Bayer AG, Germany

PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl \bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGY

Pharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

> *Escherichia coli*; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **PHARMACOLOGY**).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg•hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute

intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.

- Concurrent administration of ciprofloxacin and tizanidine (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics,) or in patients with risk factors for torsade de pointes (e.g. congenital long QTsyndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild

cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on the Liver

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE EFFECTS**). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Effects on Tendons

Tendonitis and tendon ruptures (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any sign of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

***Pseudomonas aeruginosa* Infections in Cystic Fibrosis**

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

CNS Effects

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide. If depression, psychotic reactions, suicide-related thoughts or self-injurious behaviour occur, Ciproxin should be discontinued and appropriate measures instituted.

Nervous System

Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciproxin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **ADVERSE EFFECTS**).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **ADVERSE EFFECTS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole, agomelatine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **INTERACTIONS WITH OTHER MEDICINES)**

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-

vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and

related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin in vitro potency may interfere with the Mycobacterium spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported. Quinolones may reduce the clearance of caffeine and prolong its plasma half-life, and therefore may enhance the effects of caffeine.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Other

Iron, sucralfate or highly buffered drugs (e.g. antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin; concurrent administration of these agents with Ciproxin should be avoided.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and

C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase in agomelatine exposure. Although no clinical data are available, ciprofloxacin is a moderate inhibitor of CYP450 1A2 and similar effect can be expected upon concomitant administration. Therefore concurrent use of ciprofloxacin with agomelatine is not recommended (see **PRECAUTIONS**, **Cytochrome P450**).

Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy (arthralgia, arthritis), mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema

Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and “250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON THE ARTG

2 March 1992

DATE OF MOST RECENT AMENDMENT

21 July 2017

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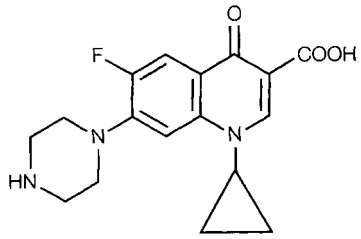
PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl\bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGY

Pharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

> *Escherichia coli*; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **PHARMACOLOGY**).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg•hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute

intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.

- Concurrent administration of ciprofloxacin and tizanidine (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see CNS effects) and musculoskeletal system (see Effects on Tendons).

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics,) or in patients with risk factors for torsade de pointes (e.g. congenital long QTsyndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on the Liver

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE EFFECTS**). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Effects on Tendons

Tendonitis and tendon ruptures (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any sign of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

***Pseudomonas aeruginosa* Infections in Cystic Fibrosis**

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

CNS Effects

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide. If depression, psychotic reactions, suicide-related thoughts or self-injurious behaviour occur, Ciproxin should be discontinued and appropriate measures instituted.

Nervous System

Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciproxin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **ADVERSE EFFECTS**).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **ADVERSE EFFECTS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole, agomelatine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **INTERACTIONS WITH OTHER MEDICINES)**

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue

nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin in vitro potency may interfere with the Mycobacterium spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported. Quinolones may reduce the clearance of caffeine and prolong its plasma half-life, and therefore may enhance the effects of caffeine.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Other

Iron, sucralfate or highly buffered drugs (e.g. antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin; concurrent administration of these agents with Ciproxin should be avoided.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and

sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase in agomelatine exposure. Although no clinical data are available, ciprofloxacin is a moderate inhibitor of CYP450 1A2 and similar effect can be expected upon concomitant administration. Therefore concurrent use of ciprofloxacin with agomelatine is not recommended (see **PRECAUTIONS**, **Cytochrome P450**).

Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy (arthralgia, arthritis), mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require

treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and “250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON THE ARTG

2 March 1992

DATE OF MOST RECENT AMENDMENT

3 November 2017

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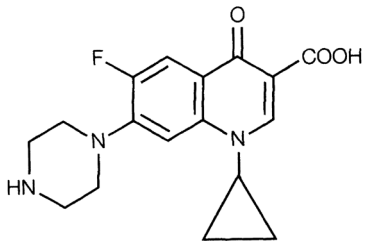
PRODUCT INFORMATION

CIPROXIN® (Ciprofloxacin)

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The CAS Registry number is [86393-32-0]. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



$\bullet HCl\bullet H_2O$

DESCRIPTION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

PHARMACOLOGY

Pharmacological actions (Microbiology)

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

> *Escherichia coli*; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **PHARMACOLOGY**).

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg.hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 μg/mL, and 4.56 μg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 μg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 μg/mL and trough concentrations range from 0.09 to 0.26 μg/mL, following two 30-minute

intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see PRECAUTIONS, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.

- Concurrent administration of ciprofloxacin and tizanidine (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see CNS effects and Psychiatric reactions) and musculoskeletal system (see Tendonitis and tendon rupture).

Streptococcus pneumoniae infections

Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (See **INTERACTIONS WITH OTHER MEDICINES)** or in patients with risk factors for QT prolongation or torsade de pointes (e.g. congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis

Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Effects on the Liver

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE EFFECTS**). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Myasthenia gravis

Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Tendonitis and tendon rupture

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. At any sign of tendonitis (e.g. painful swelling, inflammation), the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued.

Superinfections

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

***Pseudomonas aeruginosa* Infections in Cystic Fibrosis**

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion

of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions

In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

CNS Effects

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures. In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin.

Psychiatric reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciproxin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **ADVERSE EFFECTS**).

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **ADVERSE EFFECTS**).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolised via the same

enzymatic pathway (e.g. , theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole, agomelatine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **INTERACTIONS WITH OTHER MEDICINES)**

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Ciproxin. In Ciproxin-treated patients, dysglycaemia occured predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **ADVERSE EFFECTS**).

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in the presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Crystalluria

The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central nervous system adverse effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Elderly Patients

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

Impaired Renal Function

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

Effect on laboratory tests

Ciprofloxacin in vitro potency may interfere with the *Mycobacterium spp*. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of fluoroquinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported. Quinolones may reduce the clearance of caffeine and prolong its plasma half-life, and therefore may enhance the effects of caffeine.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Chelation complex formation

The simultaneous administration of Ciproxin and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. antiretrovirals) containing magnesium, aluminium or calcium reduce the absorption of ciprofloxacin. Consequently, Ciproxin should be administered either 1-2 hours before or at least 4 hours after these preparations.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by

22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase in agomelatine exposure. Although no clinical data are available, ciprofloxacin is a moderate inhibitor of CYP450 1A2 and similar effect can be expected upon concomitant administration. Therefore concurrent use of ciprofloxacin with agomelatine is not recommended (see **PRECAUTIONS**, **Cytochrome P450**).

Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy (arthralgia, arthritis), mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation,

	Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

DOSAGE AND ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

Inhalational anthrax (post-exposure) – for adults, the recommended dose is 500 mg every 12 hours. For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours. Drug administration should begin as soon as possible after suspected or confirmed exposure.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers and then treatment should be continued as prescribed. Double doses should not be taken to compensate for a missed dose.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

OVERDOSAGE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

Contact Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and "250" on the other half and the Bayer cross on bottom. Blister packs of 2 and 14 tablets.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom. Blister packs of 14.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom. Blister packs of 14.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON THE ARTG

2 March 1992

DATE OF MOST RECENT AMENDMENT

9 October 2019

® Registered Trademark of Bayer Group, Germany

AUSTRALIAN PRODUCT INFORMATION
CIPROXIN® (ciprofloxacin) tablets

1 NAME OF THE MEDICINE

Ciprofloxacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciproxin is available as 250 mg, 500 mg and 750 mg film-coated tablets for oral administration. Ciproxin 250 contains 250mg of active, Ciproxin 500 contains 500mg of active, and Ciproxin 750 contains 750mg of active.

For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Ciproxin 250 – Biconvex, white film-coated tablet round tablet 11mm in diameter containing 250 mg ciprofloxacin, the top scored and marked with "CIP" on one half of the score and "250" on the other half and the Bayer cross on bottom.

Ciproxin 500 – Biconvex, oblong 18mm x 8mm, white film-coated tablet containing 500 mg ciprofloxacin, the top scored and marked with "CIP and 500" on the other side separated by a score across the width of the tablet and "BAYER" on bottom.

Ciproxin 750 – Biconvex, 22mm x 8mm oblong, white film-coated tablet containing 750 mg ciprofloxacin, and marked with "CIP 750" on top and "BAYER" on bottom.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ciproxin is indicated for the treatment of infections caused by susceptible organisms in the conditions listed below:

Urinary tract infections

Gonorrhoeal urethritis and cervicitis

Gastroenteritis

Bronchial Infections

Skin and skin structure infections

Bone and joint infections

Chronic bacterial prostatitis of mild to moderate severity

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data.

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae.*

3. Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciproxin is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Urinary tract infections - The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as *Enterococcus faecalis*, 500 mg may be administered every 12 hours.

Bronchial infections, skin and skin structure infections - The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and joint infections - 750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea) - 500 mg every 12 hours.

Acute, uncomplicated gonorrhoeal urethritis - A single dose of 250 mg.

Chronic bacterial prostatitis - 250 to 500mg every 12 hours.

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The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

Because Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however for severe and complicated infections more prolonged therapy

may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Missed dose

If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31-60 mL/min/1.73m^2, the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2, the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

Men: $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}} x\ 0.0885$$

Women: 0.85 x the value calculated for men.

4.3 CONTRAINDICATIONS

- A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid, or any of the excipients.
- Concurrent administration of ciprofloxacin and tizanidine (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see CNS effects and Psychiatric reactions) and musculoskeletal system (see Tendonitis and tendon rupture).

Streptococcus pneumoniae infections
Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Cardiac disorders
Ciprofloxacin is associated with cases of QT prolongation (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT proglongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (See **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)** or in patients with risk factors for QT prolongation or torsade de pointes (e.g. congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Antibiotic-associated Colitis
Antibiotic-associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Myasthenia gravis
Ciproxin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Tendonitis and tendon rupture
Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with Ciproxin (ciprofloxacin) and other quinolones. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. At any sign of tendonitis (e.g. painful swelling, inflammation), the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued.

Superinfections
As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

***Pseudomonas aeruginosa* Infections in Cystic Fibrosis**
Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of

Pseudomonas aeruginosa infections in cystic fibrosis patients following a single course of the drug.

Anaphylactoid Reactions
In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.

Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciproxin should be discontinued and appropriate medical treatment given.

Phototoxicity
Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

CNS Effects
As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures. In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin.

Psychiatric reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciproxin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))**.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Cytochrome P450
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. , theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole, agomelatine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)**

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Ciproxin. In Ciproxin-treated patients, dysglycaemia occured predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (eg sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been

reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in the presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Crystalluria
The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Epileptic Patients
Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g., lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central nervous system adverse effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin should be discontinued.

Use in Hepatic Impairment

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Use in Renal Impairment

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in the Elderly

Ciproxin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**.

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Effects on Laboratory Tests

Ciprofloxacin in vitro potency may interfere with the *Mycobacterium spp*. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Theophylline

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess.

Cyclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents

Hypoglycaemia has been reported when Ciproxin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

NSAIDs

Animal studies have shown that the combination of very high doses of fluoroquinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives

On concurrent administration of Ciproxin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported. Quinolones may reduce the clearance of caffeine and prolong its plasma half-life, and therefore may enhance the effects of caffeine.

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

Chelation complex formation

The simultaneous administration of Ciproxin and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. antiretrovirals) containing magnesium, aluminium or calcium reduce the absorption of ciprofloxacin. Consequently, Ciproxin should be administered either 1-2 hours before or at least 4 hours after these preparations.

Tizanidine

Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with Ciproxin (see also **Section 4.3 CONTRAINDICATONS**).

Duloxetine

In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with Ciproxin; dose adjustment is recommended if necessary.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg Ciproxin. Therefore, caution should be used prescribing Ciproxin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase in agomelatine exposure. Although no clinical data are available, ciprofloxacin is a moderate inhibitor of CYP450 1A2 and similar effect can be expected upon concomitant administration. Therefore concurrent use of ciprofloxacin with agomelatine is not recommended (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**, **Cytochrome P450**).

Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

See **Use in Pregnancy**

Use in Pregnancy

Pregnancy Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to

ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even when taken as prescribed, this drug can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 1: Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51721, data lock point: 15 May 2005).

Common **≥1% to <10%**	**Uncommon** **≥0.1% to < 1%**	**Rare** **≥0.01% to <0.1%**	**Very rare** **<0.01%**
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual color distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyper-hidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

Note: The incidence of arthropathy (arthralgia, arthritis), mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

Table 2: ADRs derived from post marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

Table 3: The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common:	Vomiting, Transient increase in transaminases, Rash
Uncommon:	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare:	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - Calcium or magnesium containing antacids reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated from the body after haemodialysis or peritoneal dialysis.

For information on the management of overdose, contact the Poisons Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*.

Gram-Negative:

Escherichia coli; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens); Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species*; Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Gram-Positive: *

Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes (group A); Streptococcus pneumoniae; Enterococcus faecalis*.

*Note:

1. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.

3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.
4. *Enterococcus faecium*, *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.
5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker.

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally 2 -8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g., nalidixic acid, cinoxacin, etc.) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciproxin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques-either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Clinical Trials

No data available. For further information, see Section 5.1 Pharmacodynamic properties.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ciproxin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids.

Distribution

After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose-proportional manner and were, after multiple doses, as shown below:

Dose (mg)	Maximum Serum Concentration (μg/mL)	Area Under Curve (AUC) (μg.hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 μg/mL respectively.

Metabolism

Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Excretion

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 μg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 μg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of

ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION).**

Although bile concentrations of ciprofloxacin are 3 - 4 times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 µg/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**, Paediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay in vitro, but not in other mammalian systems in vitro or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any cytogenetic effect.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumours. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ciproxin tablets also contain the following excipients: microcrystalline cellulose, maize starch, colloidal anhydrous silica, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al, PP/Al, Al/Al
Pack sizes:
Ciproxin 250 – Blister packs of 2 and 14 tablets.
Ciproxin 500 – Blister packs of 2, 4, 14 and 60 tablets.
Ciproxin 750 – Blister packs of 14 and 60 tablets.

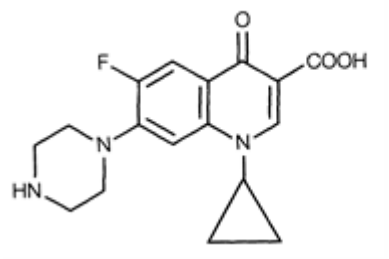
Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



.HCl.H_2O

CAS Number

86393-32-0

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.

Molecular formula	$C_{17}H_{18}FN_3O_3.HCl.H_2O$
Molecular weight	385.8
Appearance	faintly yellowish to yellow crystalline substance

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway, Pymble NSW 2073
www.bayer.com.au

9 DATE OF FIRST APPROVAL

2 March 1992

10 DATE OF REVISION

9 March 2021

Summary Table of Changes

Section Changed	Summary of New Information
All	PI reformat
4.2 Dose and method of administration	Update of PI in case of missed dose

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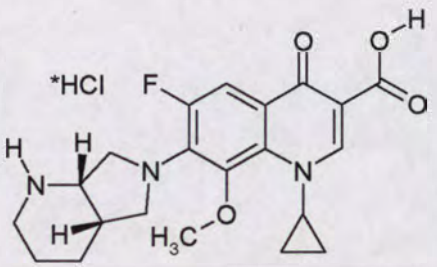
PRODUCT INFORMATION
AVELOX™
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

AVELOX (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as AVELOX tablets for oral administration, and as AVELOX IV infusion solution for intravenous administration.

AVELOX tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, AVELOX tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

AVELOX IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most

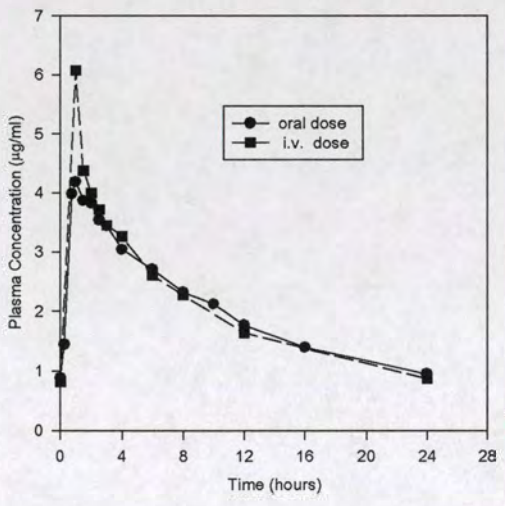
predictive for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, AVELOX can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	AUC (mg•h/L)	Half-life (hr)
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Single Dose I.V.			
Healthy young (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)		-	
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
> 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ±1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients (n = 107)		-	
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
> 65 years (n = 55)	4.7 ± 2.7		

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate (Cl_{cr} ≥ 30 and ≤ 60 mL/min) and severe (Cl_{cr} < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of AVELOX in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200

mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, AVELOX should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains)	*Klebsiella oxytoca*	*Fusobacterium spp.*
Streptococcus milleri	*Proteus mirabilis*	*Prevotella spp.*
Streptococcus mitior	*Citrobacter freundii*	*Peptostreptococcus spp.*
Streptococcus agalactiae		

Others
Legionella pneumophila
Coxiella burnetti

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the

microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

AVELOX tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	AVELOX	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of AVELOX tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	AVELOX	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	AVELOX	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		

Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO AVELOX 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared AVELOX to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared AVELOX to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for AVELOX therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for AVELOX therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in AVELOX treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all AVELOX tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, AVELOX tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	AVELOX	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups:

sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	AVELOX (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**AVELOX (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	AVELOX n/N (%)	**Comparator n/N (%)**	**AVELOX n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

AVELOX (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis

AVELOX IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

- AVELOX IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with AVELOX may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolone or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see **PRECAUTIONS**).

See also **PRECAUTIONS - General, Paediatric Use** sub-sections and **DOSAGE AND ADMINISTRATION - Paediatric** sub-section.

PRECAUTIONS

General: The safety and effectiveness of AVELOX in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See **PRECAUTIONS - Use in Pregnancy**, **Use in Lactation** and **Paediatric Use** sub-sections.

Cardiac effects: At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral AVELOX including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive AVELOX. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore AVELOX should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

AVELOX should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis: Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons: Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. AVELOX

should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS: Seizures may occur with quinolone therapy. AVELOX should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. AVELOX should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Effects on ability to drive or use machinery: AVELOX may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Paediatric Use: The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, AVELOX should not be used in paediatric patients.

Patients with severe hepatic impairment: As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of AVELOX in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential:
Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions:
Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. AVELOX should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions:
Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis:
In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with AVELOX.

Sodium content of solution for infusion:
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for

infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Interactions with other Medicines

Drugs which can affect moxifloxacin

See **CONTRAINDICATIONS** and **PRECAUTIONS** for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins: Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of AVELOX should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs: Oral doses of AVELOX should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine: The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements: When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin: No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives: No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole: Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with AVELOX and vice versa.

Digoxin: The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine: Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol: The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline: No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid: No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents: No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking AVELOX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients: To assure safe and effective use of AVELOX, the following information and instruction should be communicated to the patient when appropriate:
Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking AVELOX.
- that AVELOX tablets may be taken with or without meals, and to drink fluids liberally.

- that AVELOX tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see **PRECAUTIONS – Interactions with other Medicines** sub-section).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%	Very Rare <0.01%
Infections and Infestations				
Antibiotic induced super-infections	Mycotic superinfections			
Blood and the Lymphatic System Disorders				
Changes in blood cell counts		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia		
Changes in coagulation		Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%	Very Rare <0.01%
				abnormal
Immune System Disorders				
Acute hypersensitivity reactions		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	*Anaphylactic/ anaphylactoid shock (potentially life threatening)*
Metabolism and Nutrition Disorders				
Changes in laboratory parameters		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	
Psychiatric Disorders				
Behavioural disturbances		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation *Psychotic reactions*
Nervous system disorders				
Unspecified altered peripheral perception		Par- / Dysaesthesia	Hypoaesthesia	Hyperaesthesia
Smell and taste disorder		Taste disorder (incl. ageusia in very rare cases)	Smell disorders (incl. anosmia)	
Increased neurological activities	Headache Dizziness	Confusion and disorientation Sleep disorder Tremor Vertigo	Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical	

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%	Very Rare <0.01%
			manifestations (incl. grand mal convulsions)	✓
Decreased neurological activities		Somnolence	Disturbed attention Speech disorders Amnesia	✓
Eye Disorders				
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		✓
Ear and Labyrinth Disorders				
Ear Disorders			Tinnitus	✓
Cardiovascular System Disorders				
Repolarisation disorders	QT prolongation in patients with hypokalaemia	QT prolongation		✓
Unspecific arrhythmias		Palpitations Tachycardia		Unspecified arrhythmias ✓
Ventricular arrhythmias			Ventricular tachyarrhythmias	✓
Unspecific cardiovascular symptoms		Vasodilatation	Syncope Hypertension Hypotension	✓
Respiratory, thoracic and mediastinal Disorders				
Unspecified respiratory symptoms		Dyspnoea (including asthmatic conditions)		✓

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%	Very Rare <0.01%
Gastrointestinal Disorders				
Gastro-intestinal symptoms	Nausea Vomiting Gastrointestinal and abdominal pains	Anorexia Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis	✓
Antibiotic induced diarrhoeal disorders	Diarrhoea		Antibiotic associated colitis (in very rare cases associated with life threatening complications)	✓
Hepatobiliary Disorders				
Mild to moderate hepatic reactions	Increase in transaminases	Hepatic impairment (incl. LDH increase) ✓ Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase		✓
Severe hepatic reactions			Jaundice Hepatitis (predominantly cholestatic)	✓
Musculoskeletal, Connective Tissue and Bone Disorders ✓				

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%	Very Rare <0.01%
Tendon disorders			Tendonitis	
Unspecified joint and muscular disorders		Arthralgia Myalgia	Increased muscle tone and cramping	Arthritis
Renal and Urinary Disorders				
Renal impairment			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions				
General feeling of illness		Feeling unwell Unspecific pain Sweating		
Infusion site reactions	Injection and infusion site reactions	Infusion site (thrombo-) phlebitis		
General disorders			Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase
Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports:

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:
very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:
very rare (<0.01%): tendon rupture, gait disturbance, exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:
very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-endangering behaviour.

Nervous System Disorders:
very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:
very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:
uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

DOSAGE AND ADMINISTRATION

The usual dose of AVELOX is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. AVELOX IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see **INDICATIONS**). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with AVELOX IV may be switched to AVELOX tablets when clinically indicated at the discretion of the physician.

Directions to Administer

AVELOX IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

AVELOX IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to AVELOX IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of AVELOX IV with an infusion solution compatible with AVELOX IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, AVELOX can be taken independently from food intake.

AVELOX IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION (see Presentation and Storage Conditions).

Compatible solutions for infusion

AVELOX IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of AVELOX IV.

AVELOX IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities:
The following solutions for infusion must not be administered with AVELOX solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

Dose adjustments
Elderly: No adjustment of dose is necessary.

Paediatric: The use of AVELOX in children is not recommended (see **CONTRAINDICATIONS** and **PRECAUTIONS).**

Interethnic differences: No adjustment of dosage is required in different ethnic groups.

Hepatic impairment: No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of AVELOX in this patient group is not recommended (see also **PRECAUTIONS** for use in Child Pugh C patients).

Renal impairment: No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

AVELOX tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

AVELOX 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

AVELOX IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34mmoL sodium.

AVELOX 400 mg tablets should be stored below 25°C.
AVELOX IV solution should be stored below 30°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR:

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
™ Trademark of Bayer AG

POISON SCHEDULE OF THE MEDICINE:

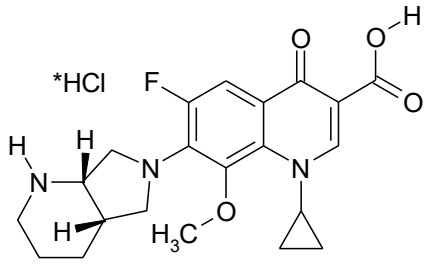
PRESCRIPTION ONLY MEDICINE

DATE OF TGA APPROVAL: 15th June 2007

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4 \cdot HCl$ and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

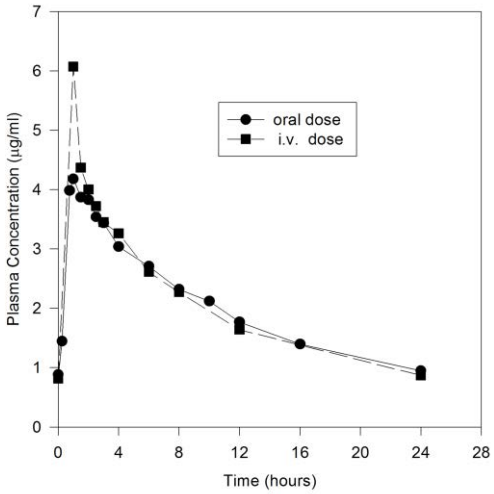
Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Single Dose I.V.			
Healthy young (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)		-	
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
> 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ±1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients (n = 107)		-	
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
> 65 years (n = 55)	4.7 ± 2.7		

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq 30$ and ≤ 60 mL/min) and severe ($Cl_{cr} < 30$ mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-

blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)

- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolone or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see **PRECAUTIONS**).

See also **PRECAUTIONS** - **General**, **Paediatric Use** sub-sections and **DOSAGE AND ADMINISTRATION** - **Paediatric** sub-section.

PRECAUTIONS

General: The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See **PRECAUTIONS** - **Use in Pregnancy**, **Use in Lactation** and **Paediatric Use** sub-sections.

Cardiac effects: At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis: Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons: Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS: Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Patients under treatment with Avelox should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see **ADVERSE EFFECTS**).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts (see **ADVERSE EFFECTS**). In the event that the patient develops these reactions, Avelox should be discontinued and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease.

Effects on ability to drive or use machinery: Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Paediatric Use: The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment: As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential:

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions:

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions:

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis:

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Sodium content of solution for infusion:

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other:

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see **Microbiology**)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See **CONTRAINDICATIONS** and **PRECAUTIONS** for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins: Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs: Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine: The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements: When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin: No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives: No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole: Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin: The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine: Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol: The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline: No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid: No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents: No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats.

Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients: To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see **INTERACTIONS WITH OTHER MEDICINES**).

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common:	Increased gamma-glutamyl-transferase
Uncommon:	Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports:

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see **INDICATIONS**). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)

Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities:

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

Dose adjustments

Elderly: No adjustment of dose is necessary.

Paediatric: The use of Avelox in children is not recommended (see **CONTRAINDICATIONS** and **PRECAUTIONS).**

Interethnic differences: No adjustment of dosage is required in different ethnic groups.

Hepatic impairment: No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also **PRECAUTIONS** for use in Child Pugh C patients).

Renal impairment: No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR:

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

POISON SCHEDULE OF THE MEDICINE:

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG:

21 December 2000

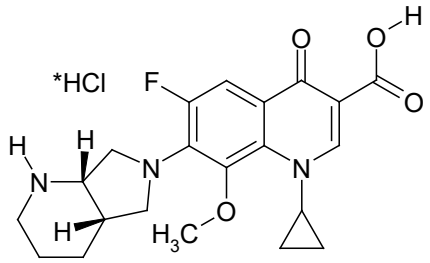
DATE OF MOST RECENT AMENDMENT:

3 July 2012

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

<u>Absorption</u>

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive

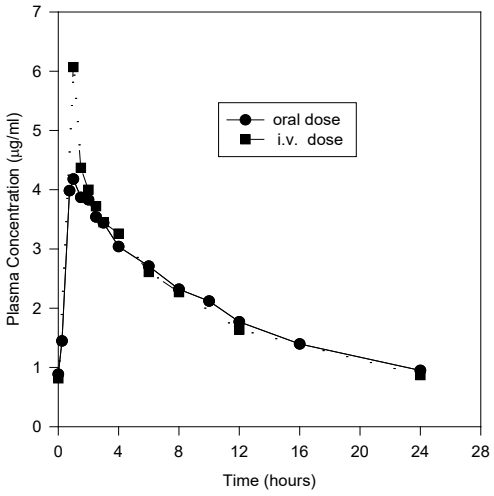
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral Healthy (n = 372)	 3.1 ± 1.0	 36.1 ± 9.1	 11.5 - 15.6*
Single Dose I.V. Healthy young (n = 56) Patients (n = 118) Male (n = 64) Female (n = 54) < 65 years (n = 58) > 65 years (n = 60)	 3.9 ± 0.9 4.4 ± 3.7 4.5 ± 2.0 4.6 ± 4.2 4.3 ± 1.3	 39.3 ± 8.6 - 	 8.2 - 15.4*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8) Healthy elderly female (n = 8) Healthy young male (n = 8) Healthy young female (n = 9)	 4.5 ± 0.5 3.8 ± 0.3 4.6 ± 0.6 3.6 ± 0.5 4.2 ± 0.5	 48.0 ± 2.7 51.8 ± 6.7 54.6 ± 6.7 48.2 ± 9.0 49.3 ± 9.5	 12.7 ±1.9
Multiple Dose I.V. Healthy young male (n = 8) Healthy elderly (n =12; 8 male, 4 female) Patients (n = 107) Male (n = 58) Female (n = 49) < 65 years (n = 52) > 65 years (n = 55)	 4.2 ± 0.8 6.1 ± 1.3 4.2 ± 2.6 4.6 ± 1.5 4.1 ± 1.4 4.7 ± 2.7	 38.0 ± 4.7 48.2 ± 0.9 - 	 14.8 ± 2.2 10.1 ± 1.6

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

PRECAUTIONS

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Patients under treatment with Avelox should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see ADVERSE EFFECTS).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts (see ADVERSE EFFECTS). In the event that the patient develops these reactions, Avelox should be discontinued and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease.

Effects on ability to drive or use machinery

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see ADVERSE EFFECTS).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Microbiology)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low

relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium),

sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C (see Presentation and Storage Conditions).

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
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875 Pacific Highway
PYMBLE NSW 2073
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POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

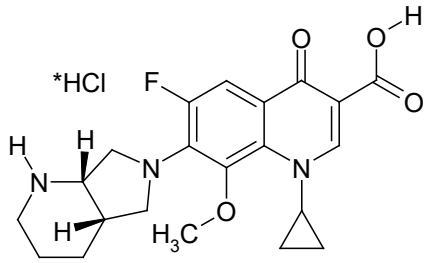
DATE OF MOST RECENT AMENDMENT

16 July 2014

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

<u>Absorption</u>

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive

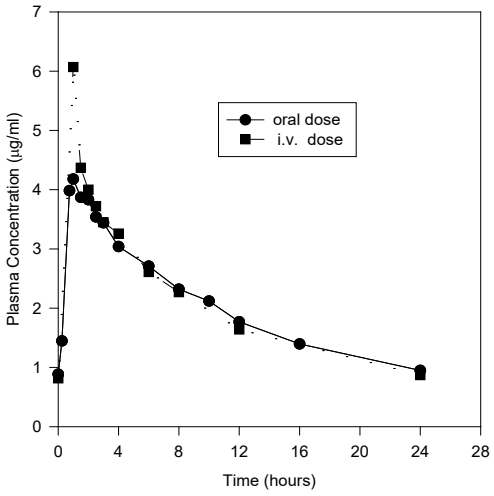
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral Healthy (n = 372)	 3.1 ± 1.0	 36.1 ± 9.1	 11.5 - 15.6*
Single Dose I.V. Healthy young (n = 56) Patients (n = 118) Male (n = 64) Female (n = 54) < 65 years (n = 58) > 65 years (n = 60)	 3.9 ± 0.9 4.4 ± 3.7 4.5 ± 2.0 4.6 ± 4.2 4.3 ± 1.3	 39.3 ± 8.6 - 	 8.2 - 15.4*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8) Healthy elderly female (n = 8) Healthy young male (n = 8) Healthy young female (n = 9)	 4.5 ± 0.5 3.8 ± 0.3 4.6 ± 0.6 3.6 ± 0.5 4.2 ± 0.5	 48.0 ± 2.7 51.8 ± 6.7 54.6 ± 6.7 48.2 ± 9.0 49.3 ± 9.5	 12.7 ±1.9
Multiple Dose I.V. Healthy young male (n = 8) Healthy elderly (n =12; 8 male, 4 female) Patients (n = 107) Male (n = 58) Female (n = 49) < 65 years (n = 52) > 65 years (n = 55)	 4.2 ± 0.8 6.1 ± 1.3 4.2 ± 2.6 4.6 ± 1.5 4.1 ± 1.4 4.7 ± 2.7	 38.0 ± 4.7 48.2 ± 0.9 - 	 14.8 ± 2.2 10.1 ± 1.6

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

PRECAUTIONS

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Patients under treatment with Avelox should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see ADVERSE EFFECTS).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts (see ADVERSE EFFECTS). In the event that the patient develops these reactions, Avelox should be discontinued and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease.

Effects on ability to drive or use machinery

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see ADVERSE EFFECTS).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Microbiology)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low

relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium),

sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).

- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of

activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
®Registered Trademark of Bayer AG

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

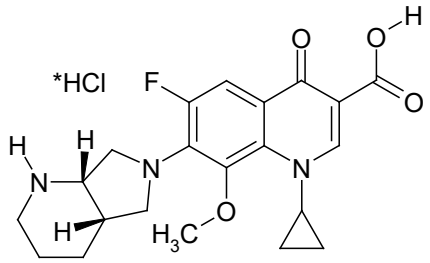
DATE OF MOST RECENT AMENDMENT

22 June 2015

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

<u>Absorption</u>

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive

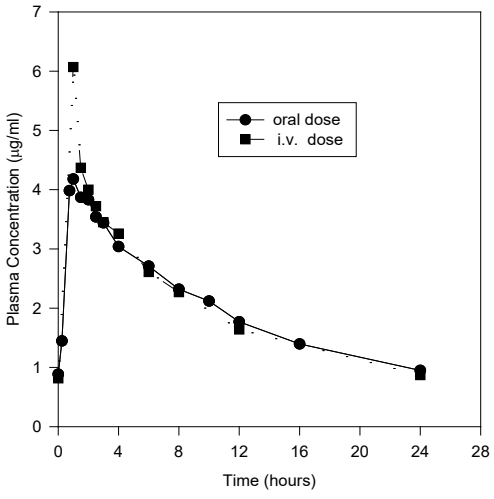
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral Healthy (n = 372)	 3.1 ± 1.0	 36.1 ± 9.1	 11.5 - 15.6*
Single Dose I.V. Healthy young (n = 56) Patients (n = 118) Male (n = 64) Female (n = 54) < 65 years (n = 58) > 65 years (n = 60)	 3.9 ± 0.9 4.4 ± 3.7 4.5 ± 2.0 4.6 ± 4.2 4.3 ± 1.3	 39.3 ± 8.6 - 	 8.2 - 15.4*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8) Healthy elderly female (n = 8) Healthy young male (n = 8) Healthy young female (n = 9)	 4.5 ± 0.5 3.8 ± 0.3 4.6 ± 0.6 3.6 ± 0.5 4.2 ± 0.5	 48.0 ± 2.7 51.8 ± 6.7 54.6 ± 6.7 48.2 ± 9.0 49.3 ± 9.5	 12.7 ±1.9
Multiple Dose I.V. Healthy young male (n = 8) Healthy elderly (n =12; 8 male, 4 female) Patients (n = 107) Male (n = 58) Female (n = 49) < 65 years (n = 52) > 65 years (n = 55)	 4.2 ± 0.8 6.1 ± 1.3 4.2 ± 2.6 4.6 ± 1.5 4.1 ± 1.4 4.7 ± 2.7	 38.0 ± 4.7 48.2 ± 0.9 - 	 14.8 ± 2.2 10.1 ± 1.6

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

PRECAUTIONS

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts (see ADVERSE EFFECTS). In the event that the patient develops these reactions, Avelox should be discontinued and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Effects on ability to drive or use machinery

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see ADVERSE EFFECTS).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Microbiology)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.

- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. .

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714

875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

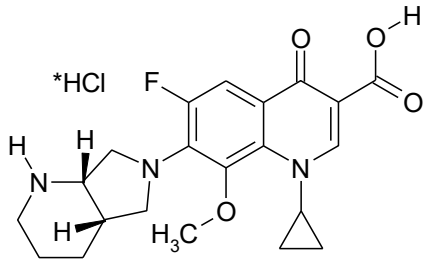
DATE OF MOST RECENT AMENDMENT

30 July 2015

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

<u>Absorption</u>

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive

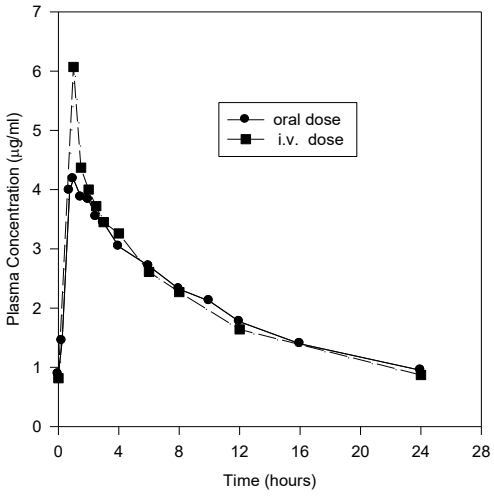
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral Healthy (n = 372)	 3.1 ± 1.0	 36.1 ± 9.1	 11.5 - 15.6*
Single Dose I.V. Healthy young (n = 56) Patients (n = 118) Male (n = 64) Female (n = 54) < 65 years (n = 58) > 65 years (n = 60)	 3.9 ± 0.9 4.4 ± 3.7 4.5 ± 2.0 4.6 ± 4.2 4.3 ± 1.3	 39.3 ± 8.6 - 	 8.2 - 15.4*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8) Healthy elderly female (n = 8) Healthy young male (n = 8) Healthy young female (n = 9)	 4.5 ± 0.5 3.8 ± 0.3 4.6 ± 0.6 3.6 ± 0.5 4.2 ± 0.5	 48.0 ± 2.7 51.8 ± 6.7 54.6 ± 6.7 48.2 ± 9.0 49.3 ± 9.5	 12.7 ±1.9
Multiple Dose I.V. Healthy young male (n = 8) Healthy elderly (n =12; 8 male, 4 female) Patients (n = 107) Male (n = 58) Female (n = 49) < 65 years (n = 52) > 65 years (n = 55)	 4.2 ± 0.8 6.1 ± 1.3 4.2 ± 2.6 4.6 ± 1.5 4.1 ± 1.4 4.7 ± 2.7	 38.0 ± 4.7 48.2 ± 0.9 - 	 14.8 ± 2.2 10.1 ± 1.6

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal

clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq$ 30 and $\leq$ 60 mL/min) and severe ($Cl_{cr} <$ 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

PRECAUTIONS

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Effects on CNS) and musculoskeletal system (see Effects on Tendons).

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The

magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Avelox should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self- injurious behavior such as suicide attempts (see ADVERSE EFFECTS). In the event that the patient develops these reactions, Avelox should be discontinued and appropriate measures instituted. Caution is recommended if Avelox is to be used in psychotic patients or in patients with a history of psychiatric disease.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Effects on ability to drive or use machinery

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see ADVERSE EFFECTS).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Microbiology)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

<u>Antacids, minerals and multi-vitamins</u>

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP

1M Sodium Chloride Injection

5% Glucose Injection, USP

Water for Injections, USP

10% Glucose for Injection, USP

Glucose 40%

Lactated Ringer's Solution for Injection

Ringer's Solution

Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%

Sodium chloride 20%

Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
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POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

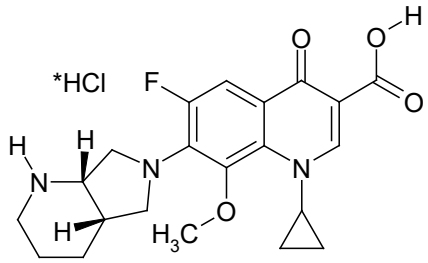
DATE OF MOST RECENT AMENDMENT

2 November 2017

PRODUCT INFORMATION
AVELOX®
(Moxifloxacin hydrochloride, BAYER)

NAME OF THE MEDICINE

Moxifloxacin hydrochloride (CAS number: 186826-86-8). Its empirical formula is $C_{21}H_{23}FN_3O_4$ * HCl and has a molecular weight of 437.9. Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(*S,S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:



DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration, and as Avelox IV infusion solution for intravenous administration.

Avelox tablets are available as a 400 mg film-coated tablet. Besides the active ingredient, Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) flexibags or glass infusion bottles, as a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability. The inactive ingredients are sodium chloride, and water for injections, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

PHARMACOLOGY

Pharmacokinetics

<u>Absorption</u>

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive

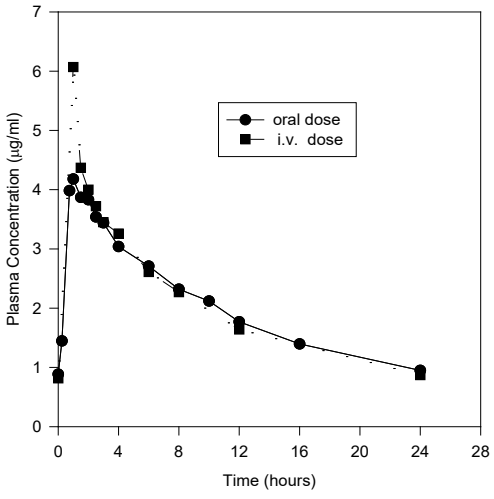
for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral Healthy (n = 372)	 3.1 ± 1.0	 36.1 ± 9.1	 11.5 - 15.6*
Single Dose I.V. Healthy young (n = 56) Patients (n = 118) Male (n = 64) Female (n = 54) < 65 years (n = 58) > 65 years (n = 60)	 3.9 ± 0.9 4.4 ± 3.7 4.5 ± 2.0 4.6 ± 4.2 4.3 ± 1.3	 39.3 ± 8.6 - 	 8.2 - 15.4*
Multiple Dose Oral Healthy young male/female (n = 15) Healthy elderly male (n = 8) Healthy elderly female (n = 8) Healthy young male (n = 8) Healthy young female (n = 9)	 4.5 ± 0.5 3.8 ± 0.3 4.6 ± 0.6 3.6 ± 0.5 4.2 ± 0.5	 48.0 ± 2.7 51.8 ± 6.7 54.6 ± 6.7 48.2 ± 9.0 49.3 ± 9.5	 12.7 ±1.9
Multiple Dose I.V. Healthy young male (n = 8) Healthy elderly (n =12; 8 male, 4 female) Patients (n = 107) Male (n = 58) Female (n = 49) < 65 years (n = 52) > 65 years (n = 55)	 4.2 ± 0.8 6.1 ± 1.3 4.2 ± 2.6 4.6 ± 1.5 4.1 ± 1.4 4.7 ± 2.7	 38.0 ± 4.7 48.2 ± 0.9 - 	 14.8 ± 2.2 10.1 ± 1.6

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (V_{ss}) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration ($\mu g/mL$)	Tissue or Fluid Concentration ($\mu g/mL$ or $\mu g/g$)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised *via* glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Elimination

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are

approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate ($Cl_{cr} \geq 30$ and ≤ 60 mL/min) and severe ($Cl_{cr} < 30$ mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Precautions for use in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg

or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See **PRECAUTIONS.**)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See **CONTRAINDICATIONS** and **PRECAUTIONS**)

Microbiology

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS** section.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains)	*Haemophilus influenzae*	*Chlamydia pneumoniae*
Staphylococcus aureus (methicillin-susceptible strains)	*Haemophilus parainfluenzae*	*Mycoplasma pneumoniae*
Streptococcus pyogenes (group A)	*Klebsiella pneumoniae*	
	Moraxella catarrhalis	
	Escherichia coli	
	Enterobacter cloacae	

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***

Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

CLINICAL TRIALS

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas
b includes infection of traumatic lesion, bite wound infection and infection with trauma.
c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia

- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics
- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see PRECAUTIONS).

See also PRECAUTIONS - General, Paediatric Use sub-sections and DOSAGE AND ADMINISTRATION - Paediatric sub-section.

PRECAUTIONS

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Pyschiatric reactions) and musculoskeletal system (see Tendonitis and tendon rupture).

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See PRECAUTIONS - Use in Pregnancy, Use in Lactation and Paediatric Use sub-sections.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the

recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Tendonitis and tendon rupture

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. At the first sign of tendonitis (e.g. painful swelling, inflammation) the

affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and Avelox should be discontinued.

Seizures

Seizures may occur with fluoroquinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), that may predispose them to seizures or lower the seizure threshold.

Myasthenia gravis

Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see ADVERSE EFFECTS).

Psychiatric reactions

Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Effects on ability to drive or use machinery

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see ADVERSE EFFECTS).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases. Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see ADVERSE EFFECTS).

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions

predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Microbiology)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Carcinogenicity and Mutagenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use In Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An

increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram, and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over–the-counter medications.
- that the recommended dose should not be exceeded.
- to inform their physician of any personal or family history of QT prolongation.
- to contact their physician if they experience palpitations or fainting spells while taking Avelox.
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally.
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see INTERACTIONS WITH OTHER MEDICINES).
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon.
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination.
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition.

INTERACTIONS WITH OTHER MEDICINES

Drugs which can affect moxifloxacin

See CONTRAINDICATIONS and PRECAUTIONS for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥ 1/100	to < 1/10
Uncommon	≥ 1/1000	to < 1/100
Rare	≥ 1/10000	to < 1/1000
Very rare	< 1/10000	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very

rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

DOSAGE AND ADMINISTRATION

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)

Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days ** (sequential IV/oral therapy*)

***** when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

**In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Directions to Administer

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Presentation and Storage Conditions).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:
0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection
Ringer's Solution
Xylitol 20%

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Incompatibilities

The following solutions for infusion must not be administered with Avelox solution for infusion:
Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%
Sodium hydrogen carbonate 8.4%

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers on the same day. Double doses should not be taken to compensate for a missed dose.

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see CONTRAINDICATIONS and PRECAUTIONS).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also PRECAUTIONS for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

OVERDOSAGE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other. Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Avelox IV 250 mL solutions (containing 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride) are available in polyolefine flexibags overwrapped with an aluminium bag or in glass bottles.

The solution for infusion (250 mL) contains 34 mmoL sodium.

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
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POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

21 December 2000

DATE OF MOST RECENT AMENDMENT

28 August 2019

AUSTRALIAN PRODUCT INFORMATION – AVELOX® (MOXIFLOXACIN HYDROCHLORIDE) TABLET AND IV SOLUTION FOR INFUSION

1 NAME OF THE MEDICINE

Moxifloxacin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Each 250 mL solution for infusion contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride. The solution for infusion (250 mL) contains 34 mmoL sodium.

3 PHARMACEUTICAL FORM

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other.

Avelox 400mg tablets contains lactose monohydrate.

Avelox IV is a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability.

For the full list of excipients, see Section 6.1 List of excipients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see Section 4.1 THERAPEUTIC INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days** (sequential IV/oral therapy*)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

** In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing

zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Method of administration

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection

Ringer's Solution
Xylitol 20%
If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers on the same day. Double doses should not be taken to compensate for a missed dose.

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

4.3 CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – General and Paediatric use and Section 4.2 DOSE AND ADMINISTRATION – Paediatric.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIOSN FOR USE - Pyschiatric reactions) and musculoskeletal system (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Tendonitis and tendon rupture).

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy and Use in lactation and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric Use.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be

used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Tendonitis and tendon rupture

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. At the first sign of tendonitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and Avelox should be discontinued.

Seizures

Seizures may occur with fluoroquinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), that may predispose them to seizures or lower the seizure threshold.

Myasthenia gravis

Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Psychiatric reactions

Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless, patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases. Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant Staphylococcus aureus (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Mechanism of action).

Moxifloxacin *in vitro* activity may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over-the-counter medications.
- that the recommended dose should not be exceeded
- to inform their physician of any personal or family history of QT prolongation
- to contact their physician if they experience palpitations or fainting spells while taking Avelox
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs which can affect moxifloxacin

See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS A D PRECAUTIONS FOR USE for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (Cmax, tmax, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased Cmax of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased Cmax (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (Cmax 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption *in vivo*. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use in pregnancy – Pregnancy Category B3

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see Section 4.8ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n=2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1000 to < 1/100
Rare ≥ 1/10000 to < 1/1000
Very rare < 1/10000

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Moxifloxacin is an 8-methoxyfluoroquinolone syntheyic antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in Section 4.1 THERAPEUTIC INDICATIONS.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains) *Staphylococcus aureus* (methicillin-susceptible strains) *Streptococcus pyogenes (group A)*	*Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Escherichia coli* *Enterobacter cloacae*	*Chlamydia pneumoniae* *Mycoplasma pneumoniae*

Moxifloxacin exhibits *in vitro* activity (MIC90 $\leq$ 2 µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila Coxiella burnetti

Moxifloxacin does not reliably show activity against Pseudomonas aeruginosa.

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. E. coli, Bacillus spp., Bacteroides vulgatus, Enterococci and Klebsiella spp. were reduced, as were the anaerobes Bifidobacterium, Eubacterium and Peptostreptococcus. These changes returned to normal within two weeks. Clostridium difficile toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Clinical trials

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an

IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were Streptococcus pneumoniae 93% (63/68), Streptococcus pneumoniae bacteremia 95% (19/20), Haemophilus influenzae 92% (23/25), Mycoplasma pneumoniae 96% (22/23), and Chlamydia pneumoniae 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for Legionella pneumophila was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	Cefuroxime axetil
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas

b includes infection of traumatic lesion, bite wound infection and infection with trauma.

c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

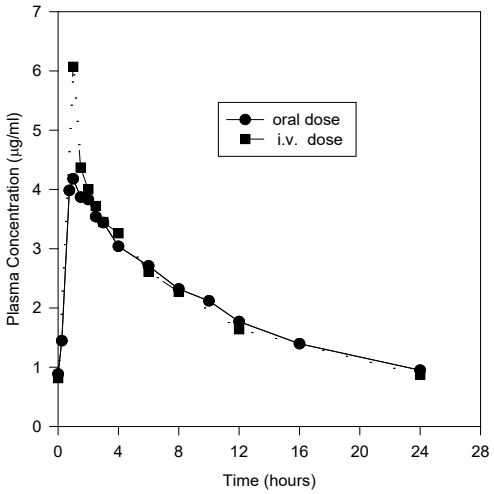
Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) Cmax and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	Cmax (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Single Dose I.V.			
Healthy young (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)		-	
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
> 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ±1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients (n = 107)		-	
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
> 65 years (n = 55)	4.7 ± 2.7		

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (Vss) is approximately 2 L/kg. In *in vitro* and ex vivo experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	**Plasma Concentration** ($\mu g / mL$)	**Tissue or Fluid Concentration** ($\mu g / mL$ **or** $\mu g / g$)	**Tissue: Plasma Ratio**
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised via glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Excretion

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, Cmax and elimination half-life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore, dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and Cmax were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate (Clcr $\geq$ 30 and $\leq$ 60 mL/min) and severe (Clcr < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost

four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Carcinogenicity

Conventional long-term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumour-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV contains the following excipients: sodium chloride, water for injections, may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

6.2 INCOMPATIBILITIES

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) polyolefine flexibags overwrapped with an aluminium bag or glass infusion bottles.

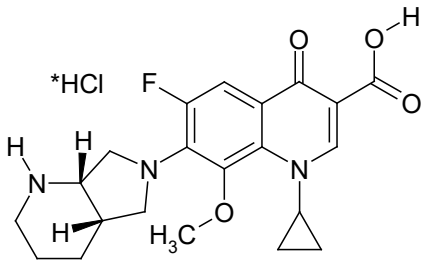
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an S,S configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(S,S)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:

Chemical structure



Chemical Formula: C21H23FN3O4 * HCl
Molecular Weight: 437.9

CAS No: 186826-86-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINE

8 SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

9 DATE OF FIRST APPROVAL

21 December 2000

10 DATE OF REVISION

28 April 2020

Summary table of changes

Section Changed	Summary of new information
All sections	Format updated to SmPC format.
6.1	Updates to spelling as per the IHIN update.

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AUSTRALIAN PRODUCT INFORMATION – AVELOX® (MOXIFLOXACIN HYDROCHLORIDE) TABLET AND IV SOLUTION FOR INFUSION

1 NAME OF THE MEDICINE

Moxifloxacin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Each 250 mL solution for infusion contains 436.8 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin in 0.8% sodium chloride. The solution for infusion (250 mL) contains 34 mmoL sodium.

3 PHARMACEUTICAL FORM

Avelox 400 mg tablets are dull red, oblong, convex film-coated tablets with BAYER on one side and M 400 on the other.

Avelox 400mg tablets contains lactose monohydrate.

Avelox IV is a sterile, preservative free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the intravenous solution is yellow. The colour does not affect, nor is it indicative of, product stability.

For the full list of excipients, see Section 6.1 List of excipients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Avelox (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis

Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults who require initial IV therapy for the treatment of infections in the conditions:

- Community acquired pneumonia (caused by susceptible organisms)
- Acute exacerbations of chronic bronchitis when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

- Avelox IV (moxifloxacin hydrochloride) intravenous solutions are indicated for treatment of adults with severe and complicated skin and skin structure infections who require initial parenteral therapy, and who have intolerance to alternative agents, (especially penicillin allergy), and when caused by organisms known to be susceptible to moxifloxacin.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with Avelox may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The usual dose of Avelox is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. Avelox IV is recommended for the treatment of adults in its approved indications who require initial IV therapy (see Section 4.1 THERAPEUTIC INDICATIONS). The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)
Major abscess of the skin and skin structure, wound infection (following surgery or trauma) and diabetic foot infection	400 mg	7-21 days** (sequential IV/oral therapy*)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

** In clinical trials in patients with major abscess of the skin and skin structure, wound infections (following surgery or trauma) and diabetic foot infection, the mean duration of intravenous therapy was approximately 6 days with an overall mean treatment duration of approximately 13 days.

The recommended duration of therapy for the treatment indication should not be exceeded.

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing

zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with Avelox IV may be switched to Avelox tablets when clinically indicated at the discretion of the physician.

Method of administration

Avelox IV (moxifloxacin) should be administered by INTRAVENOUS infusion only. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Avelox IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to Avelox IV or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of Avelox IV with an infusion solution compatible with Avelox IV as well as with other drug(s) administered via this common line.

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome etc.) the additional sodium load of the solution for infusion should be taken into account.

The extent of absorption (AUC) of moxifloxacin was not altered when administered with food. Therefore, Avelox can be taken independently from food intake.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

STORE IV SOLUTION BELOW 30°C. DO NOT STORE IV SOLUTION BELOW 15°C. DO NOT REFRIGERATE – PRODUCT PRECIPITATES AT TEMPERATURES BELOW 15°C BUT WILL RE-DISSOLVE AT ROOM TEMPERATURE (15°C - 25°C) (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE).

The solution should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

Compatible solutions for infusion

Avelox IV is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

0.9% Sodium Chloride Injection, USP
1M Sodium Chloride Injection
5% Glucose Injection, USP
Water for Injections, USP
10% Glucose for Injection, USP
Glucose 40%
Lactated Ringer's Solution for Injection

Ringer's Solution
Xylitol 20%
If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of Avelox IV.

Avelox IV is for single use in one patient only. Discard any residue. Only clear solutions are to be used.

Missed dose

Film-coated tablet: If a dose is missed, it should be taken anytime but not later than 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Dose adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Avelox in children is not recommended (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

4.3 CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or

Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – General and Paediatric use and Section 4.2 DOSE AND ADMINISTRATION – Paediatric.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIOSN FOR USE - Pyschiatric reactions) and musculoskeletal system (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Tendonitis and tendon rupture).

General

The safety and effectiveness of Avelox in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy and Use in lactation and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric Use.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Avelox including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III

(e.g. amiodarone, sotalol) antiarrhythmics, should not receive Avelox. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Avelox should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Avelox should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Tendonitis and tendon rupture

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin. This may occur even within the first 48 hours of treatment, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. At the first sign of tendonitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and Avelox should be discontinued.

Seizures

Seizures may occur with fluoroquinolone therapy. Avelox should be used with caution in patients with known or suspected CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), that may predispose them to seizures or lower the seizure threshold.

Myasthenia gravis

Avelox should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Avelox. Avelox should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the

development of an irreversible condition (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Psychiatric reactions

Fluoroquinolones, including moxifloxacin have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving moxifloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless, patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Avelox should be discontinued and appropriate therapy commenced in these cases. Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases the treatment with Avelox has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Avelox.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Avelox. In Avelox-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Sodium content of solution for infusion

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load of the solution for infusion should be taken into account. The sodium content of the solution for infusion (250 mL) is 34 mmol.

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant Staphylococcus aureus (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Mechanism of action).

Moxifloxacin *in vitro* activity may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Avelox.

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Avelox should not be used in paediatric patients.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing adverse event reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Information for Patients

To assure safe and effective use of Avelox, the following information and instruction should be communicated to the patient when appropriate:

Patients should be advised:

- that moxifloxacin may produce an effect on the electrocardiogram and may add to the effect of other drugs on the electrocardiogram. Consequently, patients should advise their physician of any other medications that they are currently taking, including over-the-counter medications.
- that the recommended dose should not be exceeded
- to inform their physician of any personal or family history of QT prolongation
- to contact their physician if they experience palpitations or fainting spells while taking Avelox
- that Avelox tablets may be taken with or without meals, and to drink fluids liberally
- that Avelox tablets should be taken at least 2 hours before or 4 hours after multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminium), sucralfate, or didanosine chewable/buffered tablets or the paediatric powder for oral solution (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- that moxifloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation or rupture of a tendon
- that moxifloxacin may cause dizziness and light-headedness, therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or co-ordination
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is any history of this condition

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs which can affect moxifloxacin

See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS A D PRECAUTIONS FOR USE for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Avelox should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Avelox should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (Cmax, tmax, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

No interaction has occurred following concomitant oral administration of moxifloxacin with oral contraceptives.

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Avelox and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased Cmax of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased Cmax (17%).

Atenolol

The pharmacokinetics of atenolol are not significantly altered by moxifloxacin. Following single dose administration in healthy subjects AUC was marginally increased (by approximately 4%) and peak concentrations were decreased by 10%.

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state during combined treatment with moxifloxacin (Cmax 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

Use of countermeasures

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption *in vivo*. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

After intravenous drug administration carbo medicinalis only slightly reduces systemic exposure (approx. 20%).

Drug-drug interactions

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Avelox should not be used with Class IA or Class III antiarrhythmics. (See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use in pregnancy – Pregnancy Category B3

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Avelox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Avelox may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see Section 4.8ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n=2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1000 to < 1/100
Rare ≥ 1/10000 to < 1/1000
Very rare < 1/10000

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/ anaphylactoid reaction Allergic oedema/ angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/ anaphylactoid shock (potentially life threatening)
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders)	
General Disorders and Administration Site Conditions	Injection and infusion site reactions	Feeling unwell Unspecific pain Sweating Infusion site (thrombo-) phlebitis	Oedema	

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

The following undesirable effects have a higher frequency in the subgroup of IV/oral sequentially treated patients:

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Moxifloxacin is an 8-methoxyfluoroquinolone syntheyic antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in Section 4.1 THERAPEUTIC INDICATIONS.

Gram-positive bacteria	***Gram-negative bacteria***	***Others***
Streptococcus pneumoniae (penicillin-susceptible strains) *Staphylococcus aureus* (methicillin-susceptible strains) *Streptococcus pyogenes (group A)*	*Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Escherichia coli* *Enterobacter cloacae*	*Chlamydia pneumoniae* *Mycoplasma pneumoniae*

Moxifloxacin exhibits *in vitro* activity (MIC90 $\leq$ 2 µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	***Gram-negative bacteria***	***Anaerobes***
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus spp.*
		Others
		Legionella pneumophila Coxiella burnetti

Moxifloxacin does not reliably show activity against Pseudomonas aeruginosa.

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the intestinal flora in humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. E. coli, Bacillus spp., Bacteroides vulgatus, Enterococci and Klebsiella spp. were reduced, as were the anaerobes Bifidobacterium, Eubacterium and Peptostreptococcus. These changes returned to normal within two weeks. Clostridium difficile toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Clinical trials

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Avelox tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Avelox tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Avelox	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)
Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Avelox	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Avelox 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Avelox to an

IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Avelox to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Avelox therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Avelox therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Avelox treated patients from these two trials were Streptococcus pneumoniae 93% (63/68), Streptococcus pneumoniae bacteremia 95% (19/20), Haemophilus influenzae 92% (23/25), Mycoplasma pneumoniae 96% (22/23), and Chlamydia pneumoniae 93% (13/14). Across all Avelox tablet and intravenous community acquired pneumonia studies, the clinical success for Legionella pneumophila was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Avelox tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Avelox	Cefuroxime axetil
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Avelox (n=180)	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID (n=187)**	**Avelox (n=315)**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID (n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas

b includes infection of traumatic lesion, bite wound infection and infection with trauma.

c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		Study 10279	
	Avelox n/N (%)	**Comparator n/N (%)**	**Avelox n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

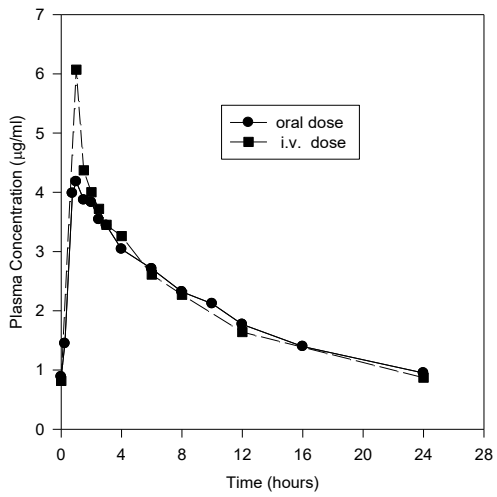
Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Avelox can be administered independent from meals.

The mean (± SD) Cmax and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	Cmax (mg/L)	**AUC (mg•h/L)**	**Half-life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Single Dose I.V.			
Healthy young (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)		-	
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
> 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ±1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients (n = 107)		-	
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
> 65 years (n = 55)	4.7 ± 2.7		

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (Vss) is approximately 2 L/kg. In *in vitro* and ex vivo experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	**Plasma Concentration** ($\mu g/mL$)	**Tissue or Fluid Concentration** ($\mu g/mL$ **or** $\mu g/g$)	**Tissue: Plasma Ratio**
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised via glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Excretion

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, Cmax and elimination half-life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore, dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and Cmax were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate (Clcr $\geq$ 30 and $\leq$ 60 mL/min) and severe (Clcr < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE in Child Pugh C patients). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost

four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Avelox in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Carcinogenicity

Conventional long-term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumour-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Avelox tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, ferric oxide, hypromellose, macrogol 4000, and titanium dioxide.

Avelox IV contains the following excipients: sodium chloride, water for injections, may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

6.2 INCOMPATIBILITIES

The following solutions for infusion must not be administered with Avelox solution for infusion:

Sodium chloride 10%
Sodium chloride 20%
Sodium hydrogen carbonate 4.2%

Sodium hydrogen carbonate 8.4%

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Avelox 400 mg tablets should be stored below 25°C.

Avelox IV solution should be stored below 30°C. Do not store below 15°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

Avelox tablets are packaged in blister strips in packs of 5 tablets and are available in one strength.

Avelox IV is available in ready-to-use 250 mL (containing 400 mg of moxifloxacin) polyolefine flexibags overwrapped with an aluminium bag or glass infusion bottles.

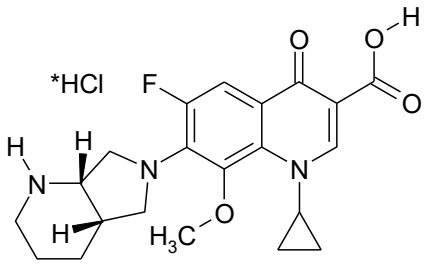
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an S,S configurated diazabicyclononyl ring moiety at the 7-position. Its chemical name is 1-cyclopropyl-7-{(S,S)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride. It is a pale yellow substance. The substance shows no melting point but it decomposes above 250°C. It is sparingly soluble in water and methanol, slightly soluble in HCl and ethanol, and practicably insoluble in acetone and toluene. It has the following chemical structure:

Chemical structure



Chemical Formula: C21H23FN3O4 * HCl
Molecular Weight: 437.9

CAS No: 186826-86-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION ONLY MEDICINE

8 SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

9 DATE OF FIRST APPROVAL

21 December 2000

10 DATE OF REVISION

21 June 2021

Summary table of changes

Section Changed	Summary of new information
4.2	Clarification for missed dose

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