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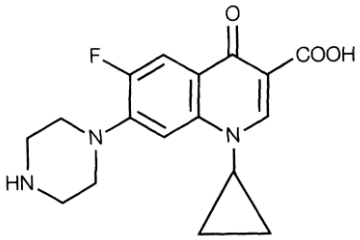
PRODUCT INFORMATION

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:



$.HCl.H_2O$

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. ~~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~~ 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~~:~~

~~29 May 2012~~

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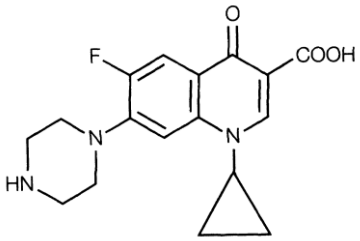
PRODUCT INFORMATION

CIPROXIN® IV
Ciprofloxacin

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 solubilising agent, hydrochloric acid for pH adjustment, and water for injections. The solution is a clear, colourless to slightly yellow solution.

PHARMACOLOGY

Pharmacological actions (Microbiology)

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*; *Moraxella* (*Branhamella*) *catarrhalis*; *Campylobacter* species.

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*.

Note: *

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

2. Most strains of streptococci are only moderately susceptible to ciprofloxacin. Clinical studies have shown the medicine 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 medicine 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 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.

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 medicines, the test should be repeated. This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of medicine 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

Distribution

Immediately following a 30-minute intravenous infusion of 200 mg ciprofloxacin, serum concentrations average 3 µg/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 is given below:

Ciprofloxacin Serum Concentrations (µg/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.

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

Protein Binding

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

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 medicine.

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.

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.

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 to1.69 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 medicine administration period.

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

3. Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolised *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 medicine 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 medicines should be considered.

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.

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 **Interaction with Other Medicines**).

PRECAUTIONS

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

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

Antibiotic-associated Colitis

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

Musculoskeletal system

Achilles and other tendon ruptures, sometimes bilateral that required surgical repair or resulted in prolonged disability have been reported with 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.

Superinfection

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 medicine.

Duration of use

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

Hypersensitivity

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.

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.

Cardiac Disorders

Ciprofloxacin is associated with cases of QT prolongation. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT prolongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant medicines 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 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).

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

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines are administered concomitantly which are metabolised 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 **Interaction with Other Medicines**).

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin IV 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 IV should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous adverse effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin IV should be discontinued.

Nervous System

Ciproxin IV might exacerbate symptoms of myasthenia gravis. 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. ~~Patients under treatment with Ciproxin IV should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness or weakness develop~~ Ciproxin IV 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**).

Use in the **Elderly**

Ciproxin IV 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 medicine, 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.

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. There

can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

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 medicine, 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 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.

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 AND STORAGE CONDITIONS** or **DOSAGE AND ADMINISTRATION** for sodium content).

Severe Infections and/or Infections due to Gram-positive or anaerobic bacteria

For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, ciprofloxacin should be used in combination with an appropriate antibacterial agent.

***Streptococcus pneumoniae* infections**

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

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 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 medicines in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin IV 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 breast 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 medicines 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.

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 medicine 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 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

Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions. This is even more applicable when the medicine is taken in conjunction with alcohol.

Interaction on Laboratory Tests

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

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin IV, 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, 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.

Omeprazole

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 and pentoxifylline (oxpentifylline). 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.

Oral antidiabetic agents

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

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 IV 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 IV with phenytoin.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives such as acenocoumarol, phenprocoumon, or fluindione. 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.

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 **CONTRAINDICATIONS**).

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 (see **PRECAUTIONS**).

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. Monitoring ropinirole-related adverse effects and/or dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

Lignocaine

It was demonstrated in healthy subjects that concomitant use of lignocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lignocaine by 22%. Although lignocaine 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 oral ciprofloxacin 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 oral ciprofloxacin 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 ciprofloxacin oral tablet. Therefore, caution should be used prescribing oral ciprofloxacin 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).

The frequencies of ADRs reported with Ciproxin IV are summarised in Table 1 below. Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

The frequencies of ADRs are defined as:
Common ≥ 1/100 to < 1/10 (≥ 1% to <10%)

Uncommon ≥ 1/1000 to < 1/100 (≥ 0.1% to <1%)
Rare ≥ 1/10000 to < 1/1000 (≥ 0.01% to <0.1%)
Very rare < 1/10000 (<0.01%)

Table 1. ADRs reported based on clinical trial data

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 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	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)

		as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	

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 Hyperaesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual colour 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) e.g. phlebitis or thrombophlebitis	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

The incidence of arthropathy is referring 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) and for which a frequency could not be estimated are listed in Table 2 below.

Table 2. ADRs reported based on post marketing reports

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)

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

Table 3. Higher frequency of adverse effects occurring in patients

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.

Table 4. 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
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.

Ciproxin 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 medicine, each medicine should be given separately in accordance with the recommended dosage and route of administration for each medicine.

Compatibility and Stability

Ciprofloxacin solutions are incompatible with all infusion solutions/medicines (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.

The visual signs of incompatibility are e.g. precipitation, clouding and discolouration. Only clear solutions are to be used.

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. Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required to prevent crystalluria. Adequate hydration must be maintained.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

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

PRESENTATION AND STORAGE CONDITIONS

Ciproxin IV 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.

Store below 30°C. Protect from light. Do not refrigerate or freeze.

Instructions for handling

At 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
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON ARTG: 20 DECEMBER 1993

DATE OF MOST RECENT AMENDMENT: ~~29 May 2012~~

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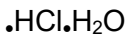
PRODUCT INFORMATION

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:



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			
	Headache	Par- and	Migraine

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
	Dizziness Sleep disorders Taste disorders	Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	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 (potentially life-threatening)

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
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

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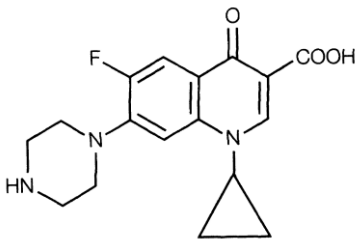
PRODUCT INFORMATION

CIPROXIN® IV
Ciprofloxacin

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 solubilising agent, hydrochloric acid for pH adjustment, and water for injections. The solution is a clear, colourless to slightly yellow solution.

PHARMACOLOGY

Pharmacological actions (Microbiology)

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*; *Moraxella* (*Branhamella*) *catarrhalis*; *Campylobacter* species.

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*.

Note: *

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

2. Most strains of streptococci are only moderately susceptible to ciprofloxacin. Clinical studies have shown the medicine 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 medicine 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 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.

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 medicines, the test should be repeated. This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of medicine 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

Distribution

Immediately following a 30-minute intravenous infusion of 200 mg ciprofloxacin, serum concentrations average 3 µg/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 is given below:

Ciprofloxacin Serum Concentrations (µg/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.

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

Protein Binding

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

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 medicine.

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.

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.

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 to1.69 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 medicine administration period.

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

3. Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolised *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 medicine 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 medicines should be considered.

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.

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 **Interaction with Other Medicines**).

PRECAUTIONS

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

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

Antibiotic-associated Colitis

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

Musculoskeletal system

Achilles and other tendon ruptures, sometimes bilateral that required surgical repair or resulted in prolonged disability have been reported with 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.

Superinfection

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 medicine.

Duration of use

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

Hypersensitivity

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.

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.

Cardiac Disorders

Ciprofloxacin is associated with cases of QT prolongation. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT prolongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant medicines 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 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).

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

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines are administered concomitantly which are metabolised 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 **Interaction with Other Medicines**).

Epileptic Patients

Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower seizure threshold. Ciproxin IV 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 IV should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous adverse effects. Cases of status epilepticus have been reported. If seizures occur, Ciproxin IV should be discontinued.

Nervous System

Ciproxin IV might exacerbate symptoms of myasthenia gravis. 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 IV 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**).

Use in the **Elderly**

Ciproxin IV 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 medicine, 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.

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

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 medicine, 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 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.

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 AND STORAGE CONDITIONS** or **DOSAGE AND ADMINISTRATION** for sodium content).

Severe Infections and/or Infections due to Gram-positive or anaerobic bacteria

For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, ciprofloxacin should be used in combination with an appropriate antibacterial agent.

***Streptococcus pneumoniae* infections**

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

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 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 medicines in its class, ciprofloxacin causes arthropathy in immature animals.

Ciproxin IV 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 breast 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 medicines 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.

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 medicine 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 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

Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions. This is even more applicable when the medicine is taken in conjunction with alcohol.

Interaction on Laboratory Tests

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

INTERACTIONS WITH OTHER MEDICINES

Drugs known to prolong QT interval

Ciproxin IV, 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, 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.

Omeprazole

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 and pentoxifylline (oxpentifylline). 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.

Oral antidiabetic agents

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

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 IV 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 IV with phenytoin.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives such as acenocoumarol, phenprocoumon, or fluindione. 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.

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 **CONTRAINDICATIONS**).

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 (see **PRECAUTIONS**).

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. Monitoring ropinirole-related adverse effects and/or dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

Lignocaine

It was demonstrated in healthy subjects that concomitant use of lignocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lignocaine by 22%. Although lignocaine 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 oral ciprofloxacin 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 oral ciprofloxacin 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 ciprofloxacin oral tablet. Therefore, caution should be used prescribing oral ciprofloxacin 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).

The frequencies of ADRs reported with Ciproxin IV are summarised in Table 1 below. Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

The frequencies of ADRs are defined as:

Common	≥ 1/100 to < 1/10 (≥ 1% to <10%)
Uncommon	≥ 1/1000 to < 1/100 (≥ 0.1% to <1%)
Rare	≥ 1/10000 to < 1/1000 (≥ 0.01% to <0.1%)
Very rare	< 1/10000 (<0.01%)

Table 1. ADRs reported based on clinical trial data

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	Haemolytic anaemia Agranulocytosis

		Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	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 hyper-activity / 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 Hyperaesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual colour 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) e.g. phlebitis or thrombophlebitis	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	

The incidence of arthropathy is referring 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) and for which a frequency could not be estimated are listed in Table 2 below.

Table 2. ADRs reported based on post marketing reports

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)

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

Table 3. Higher frequency of adverse effects occurring in patients

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.

Table 4. 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
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.

Ciproxin 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 medicine, each medicine should be given separately in accordance with the recommended dosage and route of administration for each medicine.

Compatibility and Stability

Ciprofloxacin solutions are incompatible with all infusion solutions/medicines (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.

The visual signs of incompatibility are e.g. precipitation, clouding and discolouration. Only clear solutions are to be used.

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. Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required to prevent crystalluria. Adequate hydration must be maintained.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

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

PRESENTATION AND STORAGE CONDITIONS

Ciproxin IV 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.

Store below 30°C. Protect from light. Do not refrigerate or freeze.

Instructions for handling

At 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
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION ON ARTG: 20 DECEMBER 1993

DATE OF MOST RECENT AMENDMENT:

® Registered Trade Mark of Bayer AG, Germany

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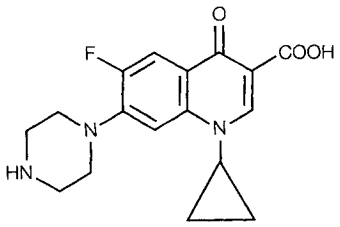
PRODUCT INFORMATION

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	
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~~xx xxxxxx xxxx

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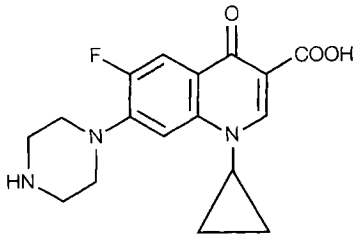
PRODUCT INFORMATION

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	
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

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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.

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 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 prolongation 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 (e.g. 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.

Levothyroxine

Oral ciprofloxacin may decrease the absorption of levothyroxine. An interval of 6 hours between the administration of the two medications is 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)

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)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
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.

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.

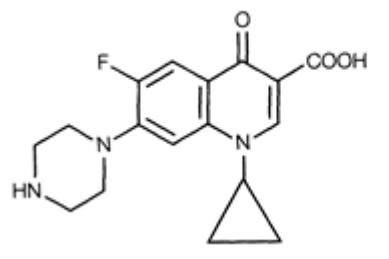
Some strengths, pack sizes and/or pack types may not be marketed.

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~~TBC

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~~
4.5	Addition of drug interaction information with Levothyroxine

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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.

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 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 prolongation 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 (e.g. 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.

Levothyroxine

Oral ciprofloxacin may decrease the absorption of levothyroxine. An interval of 6 hours between the administration of the two medications is 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)

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)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis

Common ≥1% to <10%	Uncommon ≥0.1% to < 1%	Rare ≥0.01% to <0.1%	Very rare <0.01%
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.

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.

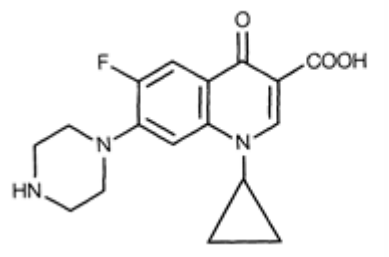
Some strengths, pack sizes and/or pack types may not be marketed.

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

TBC

Summary Table of Changes

Section Changed	Summary of New Information
4.5	Addition of drug interaction information with Levothyroxine

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