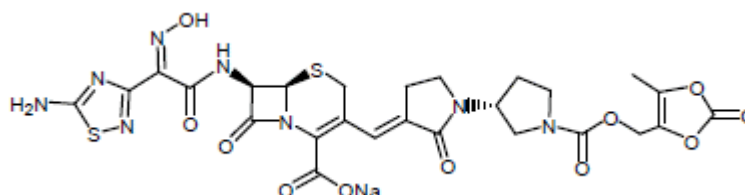# PRODUCT INFORMATION

Zevtera[â] 667 mg (ceftobiprole medocaril sodium) Powder for injection

NAME OF THE MEDICINE

Ceftobiprole medocaril sodium, which is a prodrug for ceftobiprole (the active moiety).

The chemical structure of ceftobiprole medocaril sodium is:

The chemical name of ceftobiprole medocaril sodium is (6R,7R)-7-[[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetyl]amino]-3 [(E)-[(3'R)-1'-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy]carbonyl]-2-oxo[1,3'-bipyrrolidin]-3-ylidene]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, monosodium salt.

Molecular formula: $C_{26}H_{25}N_8NaO_{11}S_2$

Molecular weight: 712.64

CAS number: 252188-71-9

DESCRIPTION

Ceftobiprole medocaril sodium is a semi-synthetic pro-drug from the cephalosporin class of β-lactam antibiotics. It is freely soluble in water. A formulation-relevant pKa value of 2.8 at 25°C for the carboxylic acid moiety of ceftobiprole medocaril sodium is measured at low concentration (0.1 mg/mL). The estimate of the pKa for dissociation of the carboxylic acid is 1.8 and 2.0 at 25°C and 5°C, respectively. The pKa asssociated with the oxime functional group is around 9.

ZEVTERA powder for injection is a sterile lyophilised powder. It is a white, yellowish to slightly brownish, cake to broken cake or powder. Each vial contains 666.6 mg of ceftobiprole medocaril sodium (equivalent to 500.0 mg of ceftobiprole, the active moiety), 26.3 mg citric acid monohydrate and sodium hydroxide in sufficient quantities for pH adjustment. The pH of the reconstituted solution is between 4.5 and 5.5.

PHARMACOLOGY

Mechanism of Action

Ceftobiprole exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs) in susceptible species. In Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), ceftobiprole binds to PBP2a. Ceftobiprole has demonstrated *in vitro* activity against strains with divergent *mecA* homolog (*mecC or mecALGA251*). Ceftobiprole also binds to PBP2b in *Streptococcus pneumoniae* (penicillin-intermediate), PBP2x in S. *pneumonia* (penicillin resistant), and to PBP5 in *Enterococcus faecalis*.

Mechanism of Resistance

Ceftobiprole is inactive against strains of Enterobacteriaceae that express Ambler class A β-lactamases, especially TEM, SHV and CTX-M type extended-spectrum β-lactamases (ESBL) and the KPC-type carbapenemases, Ambler class B β-lactamases and Ambler class D β-lactamases, especially ESBL variants and carbapenemases (OXA-48). Ceftobiprole is also inactive against strains that have high levels of expression of Ambler class C β-lactamases.

Ceftobiprole is inactive against strains of *P. aeruginosa* that express enzymes belonging to Ambler class A (e.g., PSE-1), Ambler class B (e.g., IMP-1, VIM-1, VIM-2) and Ambler class D (e.g., OXA-10). It is also inactive against isolates that have acquired mutations in regulatory genes leading to de-repressed levels of expression of the chromosomal Ambler class C β-lactamase, or over-expression of the Mex XY efflux pump.

Ceftobiprole is inactive against strains of *Acinetobacter* spp. that express enzymes belonging to Ambler class A (e.g., VEB-1), Ambler class B (e.g., IMP-1, IMP-4) Ambler class D (e.g., OXA-25, OXA-26), or that have de-repressed levels of expression of the chromosomal Ambler class C β-lactamase.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	MIC breakpoints (mg/L)	
Pathogen	Susceptible (≤ S)	Resistant (R >)
Staphylococcus aureus (including MRSA)	2	2
Streptococcus pneumoniae	0.5	0.5
Enterobacteriaceae	0.25	0.25
Pseudomonas aeruginosa	IE[a]	IE[a]
Non-species specific breakpoint[b]	4	4
[a] Insufficient evidence.		
[b] Based on the PK/PD target for Gram-negative organisms.		

Pharmacokinetic/pharmacodynamics relationship

As with other beta-lactam antimicrobial agents, the percent time above the minimum inhibitory concentration (MIC) of the infecting organism over the dosing interval (%T > MIC) has been shown to be the parameter that best correlates with the efficacy of ceftobiprole.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the following pathogens in patients with Hospital-acquired pneumonia (HAP) (not including ventilator-associated pneumonia (VAP) and community-acquired pneumonia (CAP) that were susceptible to ceftobiprole *in vitro*:

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus pneumoniae* (including MDRSP)
- *Escherichia coli*
- *Klebsiella pneumonia*

Antibacterial activity against other relevant pathogens

Clinical efficacy has not been established against the following pathogens, although *in vitro* studies suggest that they would often be susceptible to ceftobiprole in the absence of an acquired mechanism of resistance:

- *Acinetobacter* spp.
- *Citrobacter* spp.
- *Enterobacter* spp.
- *Haemophilus influenzae*
- *Klebsiella oxytoca*
- *Moraxella catarrhalis*
- *Morganella morganii*
- *Proteus mirabilis*
- *Providencia* spp.
- *Pseudomonas* spp.
- *Serratia* spp.

In vitro data indicate that the following species are not susceptible to ceftobiprole:

- *Chlamydophila (Chlamydia) pneumoniae*
- *Burkholderia cepacia complex*
- *Mycoplasma pneumoniae*
- *Mycobacteria*
- *Nocardia spp*
- *Stenotrophomonas maltophilia*

Pharmacokinetic properties

Plasma concentrations

The mean pharmacokinetic parameters of Zevtera in adults for a single 666.6 mg dose administered as a 2-hour infusion and multiple 666.6 mg doses administered every 8 hours as 2-hour infusions are summarised in Table 1. Pharmacokinetic characteristics were similar with single and multiple dose administration.

Table 1: Mean (standard deviation) pharmacokinetic parameters of Zevtera in adults

Parameter	Single 666.6 mg dose administered as a 120-minute infusion	Multiple 666.6 mg doses administered every 8 hours as 120 minute infusions
C_{max} (mg/mL)	29.2 (5.52)	33.0 (4.83)
AUC (mg· h/mL)	90.0 (12.4)	102 (11.9)
$t_{1/2}$ (hours)	3.1 (0.3)	3.3 (0.3)
CL (mL/min)	4.89 (0.69)	4.98 (0.58)

Distribution

Ceftobiprole binds minimally (16%) to plasma proteins and binding is independent of concentration. Ceftobiprole steady-state volume of distribution (18 litres) approximates extracellular fluid volume in humans.

Metabolism

Conversion of the pro-drug ceftobiprole medocaril sodium, to the active moiety ceftobiprole, occurs rapidly and is mediated by non-specific plasma esterases. Pro-drug concentrations are negligible and are measurable in plasma and urine only during infusion. The metabolite resulting from the cleavage of the pro-drug is diacetyl which is an endogenous human compound.

Ceftobiprole undergoes minimal metabolism to the open-ring metabolite, which is shows no antimicrobial activity. Systemic exposure to the open-ring metabolite was considerably lower than for ceftobiprole, accounting for approximately 4% of the parent exposure in subject with a normal renal function.

In vitro studies demonstrated that ceftobiprole is an inhibitor of the hepatocyte uptake transporters OATP1B1 and OATP1B3, but is not an inhibitor of P-gp, BCRP, MDR1, MRP2, OAT1, OAT3, OCT1 or OCT2. Ceftobiprole is potentially a weak substrate of the renal tubule cells uptake transporters OAT1 and OCT2.

Ceftobiprole is not a P-gp inhibitor or substrate. The potential for other drugs to interact with ceftobiprole is minimal, since only a small fraction of ceftobiprole is metabolised. Therefore, no relevant drug-drug interactions are anticipated.

Since ceftobiprole does not undergo tubular secretion and only a fraction is reabsorbed, renal drug-drug interactions are not expected.

Excretion

Ceftobiprole is eliminated primarily unchanged by renal excretion, with a half-life of approximately 3 hours. The predominant mechanism responsible for elimination is glomerular filtration, with some active reabsorption. Following single dose administration in human, approximately 89% of the administered dose is recovered in the urine as active ceftobiprole (83%), the open-ring metabolite (5%) and ceftobiprole medocaril (<1%).

Linearity / Non-linearity

Ceftobiprole exhibits linear and time-independent pharmacokinetics. The C_{max} and AUC of Zevtera increase in proportion to dose over a range of 125 mg to 1 g. Steady-state active substance concentrations are attained on the first day of dosing; no appreciable accumulation occurs with every-8-hour dosing in subjects with normal renal function.

Special Populations

Renal impairment
The estimation of creatinine clearance should be based on the Cockcroft-Gault formula using actual body weight. During treatment with ceftobiprole it is recommended that an enzymatic method of measuring serum creatinine be used.

The pharmacokinetics of ceftobiprole are similar in healthy volunteers and subjects with mild renal impairment (CL_{CR} 50 to 80 mL/min). Ceftobiprole AUC was 2.5- and 3.3-fold higher in subjects with moderate (CL_{CR} 30 to < 50 mL/min) and severe (CL_{CR} < 30 mL/min) renal impairment, respectively, than in healthy subjects with normal renal function. Dosage adjustment is recommended in patients with moderate to severe renal impairment.

End-stage renal disease requiring dialysis
AUCs of ceftobiprole and of the microbiologically inactive ring-opened metabolite are substantially increased in patients with end stage renal disease who require haemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease on haemodialysis received a single dose of 250 mg Zevtera by intravenous infusion, ceftobiprole was demonstrated haemodialysable with an extraction ratio of 0.7.

Patients with creatinine clearance > 150mL/min
Ceftobiprole systemic clearance (CL_{SS}) was 40% greater in subjects with a CL_{CR} > 150 mL/min compared to subjects with a normal renal function (CL_{CR} = 80-150 mL/min). Volume of distribution was 30% larger. In this population, based on pharmacokinetic/pharmacodynamic considerations, prolongation of duration of infusion is recommended.

Hepatic impairment
The pharmacokinetics of ceftobiprole in patients with hepatic impairment have not been established. As ceftobiprole undergoes minimal hepatic metabolism and is predominantly excreted unchanged in the urine, the clearance of Zevtera is not expected to be affected by hepatic impairment.

Elderly
Population pharmacokinetic data showed that age as an independent parameter has no effect on the pharmacokinetics of ceftobiprole. Dosage adjustment is not considered necessary in elderly patients with normal renal function.

Gender
Systemic exposure to ceftobiprole was higher in females than males (21% for C_{max} and 15% for AUC), however the %T>MIC was similar in both males and females. Therefore, dosage adjustments based on gender are not considered necessary.

Race
Population pharmacokinetic analyses (including Caucasians, Black and Other groups) and a dedicated pharmacokinetic study in healthy Japanese subjects showed no effect of race on the pharmacokinetics of ceftobiprole. Therefore, dosage adjustments based on race are not considered necessary.

Body weight
A study was performed in morbidly obese subjects. No dose adjustments based on body weight are required.

CLINICAL TRIALS

Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)

The efficacy and safety of Zevtera in patients with hospital-acquired pneumonia was established in a double-blind, randomized, multi-centre, adequately powered, well-controlled Phase 3 non-inferiority study (BAP248/307). HAP subjects were randomly assigned to treatment for 7 to 14 days with either ceftobiprole (0.5 g every 8 hours as a 2-hour infusion) or a combination of ceftazidime (2 g every 8 hours as an atypical prolonged 2-hour infusion) and linezolid (0.6 g every 12 hours as a 1-hour infusion). The study included 781 subjects in the intent-to-treat (ITT) analysis set. This study included a subset of 210 subjects with VAP.

Study population

The percentage of male subjects in the ceftobiprole group was 71% and 62% in the comparator group. The percentage of subjects who were aged ≥ 65 years was 46.9% and the racial composition of the study populations the percentage of Asian subjects was 12.2% and the percentage of 'other' subjects (i.e., not white, black, or Asian) was 3.6%.

Study results

The study achieved its primary objective of demonstrating non-inferiority of ceftobiprole compared with ceftazidime plus linezolid for clinical cure rate at the TOC visit (Table 2).

Table 2   Clinical cure rate at TOC visit (primary endpoint) in study BAP248/307

Analysis set Group	Ceftobiprole		Linezolid/ceftazidime		Diff. (%)[a]	95% CI [#]
	N	n (%)	N	n (%)		
Intent-to-Treat						
All subjects	**391**	**195 (49.9)**	**390**	**206 (52.8)**	**(−2.9)**	**(−10.0; 4.1)**
NP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	(0.8)	(−7.3; 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	(−13.7)	(−26.0; −1.5)
Clinically Evaluable						
All subjects	**251**	**174 (69.3)**	**244**	**174 (71.3)**	**(−2.0)**	**(−10.0; 6.1)**
NP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	(1.6)	(−6.9; 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	(−18.2)	(−36.4; −0.0)

n is the number of subjects with clinical cure at the TOC visit.

[a] Difference ceftobiprole minus linezolid/ceftazidime.

[b] Difference ceftobiprole minus ceftriaxone with orwithout linezolid.

[#] Two-sided 95% CI is based on the Normal approximation to the difference of the two proportions.

In the subset of subjects with ventilator-associated pneumonia (VAP), the clinical cure and microbiological eradication rates were lower and all-cause mortality numerically higher in the ceftobiprole group than in the comparator (linezolid/ceftazidime) group.

Community acquired pneumonia (CAP)

The efficacy and safety of ceftobiprole in patients with CAP was established in a double-blind, randomized, multi-centre, adequately powered, well-controlled Phase 3 non-inferiority study (CAP-3001). CAP subjects were randomly assigned to treatment for 5 to 14 days (target of 7 days) with either ceftobiprole (0.5 g every 8 hours as a 2-hour infusion) or ceftriaxone (2 g once daily as a 30-minute infusion) with or without linezolid (0.6 g every 12 hours as a 1-hour infusion). The study included 638 subjects in the ITT analysis set.

Study population

Patients in Study CAP-3001 must have had a diagnosis of pneumonia acquired in the community and severe enough to require hospitalization and treatment with intravenous antibiotics for at least 3 days. The percentage of subjects who were aged ≥ 65 years was 35.5%; and the percentage of Asian subjects was 21.0% and the percentage of 'other' subjects (i.e., not white, black, or Asian) was 14.2%.

Study results

Study CAP-3001 met its primary objective of demonstrating non-inferiority of ceftobiprole compared with ceftriaxone with or without linezolid (Table 3).

Table 3   Clinical cure rate at TOC visit (primary endpoint) in study CAP-3001

Analysis set Group	Ceftobiprole		Ceftriaxone ± linezolid		Diff. (%)[b]	95% CI [#]
	N	n (%)	N	n (%)		
Intent-to-Treat						
All subjects	**314**	**240 (76.4)**	**324**	**257 (79.3)**	**(−2.9)**	**(−9.3; 3.6)**
PORT Risk Classes ≥ III	158	125 (79.1)	149	117 (78.5)	(0.6)	(−8.6; 9.7)
PORT Risk Classes ≥ IV	69	56 (81.2)	72	56 (77.8)	(3.4)	(−9.9; 16.7)
Clinically Evaluable						
All subjects	**231**	**200 (86.6)**	**238**	**208 (87.4)**	**(−0.8)**	**(−6.9; 5.3)**
PORT Risk Classes ≥ III	126	109 (86.5)	117	101 (86.3)	(0.2)	(−8.4; 8.8)
PORT Risk Classes ≥ IV	51	46 (90.2)	58	49 (84.5)	(5.7)	(−6.7; 18.1)

n is the number of subjects with clinical cure at the TOC visit.

[a] Difference ceftobiprole minus linezolid/ceftazidime.

[b] Difference ceftobiprole minus ceftriaxone with or without linezolid.

[#] Two-sided 95% CI is based on the Normal approximation to the difference of the two proportions.

In an additional analysis, the non-inferiority of ceftobiprole was further demonstrated for CAP subjects in PORT Risk Classes ≥ III. Disease severity was assessed using the PSI score (PORT Risk Class). 22% (141/638) of subjects had a PSI score ≥ 91, and 48% (307/638) of patients were in PORT Risk Class III–V. Non-inferiority of ceftobiprole was demonstrated in this patients (Table 4).

Table 4   Results of study CAP-3001: analyses for PORT Risk Classes III–V

	Ceftobiprole		Ceftriaxone ± linezolid		Diff (%)	95% CI [#]
	N	n (%)	N	n (%)		
Primary endpoint subgroup analyses						
Clinical cure at TOC for subjects in PORT Risk Classes III–V						
PORT Risk Class III, IV or V ITT	157	125 (79.6)	149	117 (78.5)	(1.1)	(−8.0; 10.2)
PORT Risk Class III, IV or V Clinically Evaluable	126	109 (86.5)	117	101 (86.3)	(0.2)	(−8.4; 8.8)
Secondary endpoint subgroup analyses						
Microbiological eradication at TOC for subjects in PORT Risk Classes III–V						
PORT Risk Class III, IV or V Microbiological ITT	54	43 (79.6)	39	29 (74.4)	(5.3)	(−12.1%; 22.7%)
PORT Risk Class III, IV or V Microbiologically Evaluable	45	39 (86.7)	30	26 (86.7)	0	(−15.7%; 15.7%)

[#] Two-sided 95% CI is based on the Normal approximation to the difference of the two proportions.

Microbiological eradication

Zevtera demonstrated high microbiological success rates and was efficacious against HAP and CAP caused by *S. aureus* and other common HAP and CAP pathogens (see Table 5).

Table 5   Microbiological eradication rates by pathogen in HAP (excluding VAP) and CAP subjects

Pathogen[*]	HAP (excluding VAP) (study BAP248/307) n/N (%)		CAP (study CAP-3001) n/N (%)	
	Ceftobiprole	Linezolid/ ceftazidime	Ceftobiprole	Ceftriaxone (+linezolid)
S. aureus (MSSA)	15/20 (75)	21/30 (70)	6/6 (100)	6/6 (100)
S. aureus (MRSA)	8/19 (42)	10/19 (53)	1/1 (100)	na
S. pneumoniae (including MDRSP)	7/7 (100)	13/14 (93)	26/28 (93)	33/36 (92)
E. coli	8/14 (57)	7/11 (64)	6/6 (100)	0/0 (0)
H. influenzae	2/3 (33)	5/5 (100)	7/7 (100)	13/14 (93)
K. pneumoniae	10/12 (83)	15/19 (79)	4/5 (80)	7/7 (100)
P. aeruginosa	9/16 (56)	11/20 (55)	0/1	2/2 (100)

INDICATIONS

Zevtera (ceftobiprole medocaril sodium) is indicated for the treatment of the following infections in adults suspected or proven to be caused by designated susceptible microorgansims:

· Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
· Community-acquired pneumonia (CAP)

Consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

Hypersensitivity to the active substance (ceftobiprole medocaril sodium) or excipients (citric acid monohydrate and sodium hydroxide).

Hypersensitivity to the cephalosporin class of antibiotics.

Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibiotic (e.g. penicillins or carbapenems).

PRECAUTIONS

Hypersensitivity Reactions

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible (see *Contraindications* and *Adverse effects*). In case of severe hypersensitivity

reactions, treatment with Zevtera must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to Zevtera, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if Zevtera is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Clostridium difficile-associated diarrhoea

Antibacterial agent-associated colitis and pseudomembranous colitis have been reported with the use of Zevtera and may range in severity from mild to life-threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of Zevtera (see *Adverse effects*). Discontinuation of therapy with Zevtera and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with pre-existing seizure disorders

Seizures have been associated with the use of Zevtera. Seizures occurred most commonly in patients with pre-existing CNS/seizure disorders during treatment with Zevtera. Therefore caution is advised when treating these patients.

Dosing above the recommended dose range

There is no clinical experience with Zevtera doses higher than the recommended 666.6 mg administered every eight hours.

Superinfection with non-susceptible organisms

The use of Zevtera may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if evidence of superinfection occurs during therapy.

Renal toxicity in animals

In animals, reversible renal toxicity was observed at high doses of Zevtera and was associated with precipitation of drug-like material in the distal tubules. Although the clinical significance of this observation is unknown, it is advisable to correct hypovolaemia to maintain normal urinary output in patients receiving Zevtera.

Precipitation with calcium-containing solutions

Precipitation can occur when Zevtera is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, Zevtera and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line (see *Incompatabilities with other medicines*).

Limitations of clinical data

There is no experience with ceftobiprole in the treatment of HAP (excluding VAP) and CAP in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with

myelosuppression. Caution is advised when treating such patients.

Patients with ventilator-associated pneumonia (VAP)

Zevtera has not been shown to be effective in the treatment of patients with VAP. Zevtera should not be initiated in patients with VAP (see *Pharmacodynamic Properties*). In addition, on the basis of a post-hoc analysis showing a trend in favour of ceftobiprole, it is recommended that in patients with hospital-acquired pneumonia (HAP) who subsequently require ventilation, Zevtera should be used with caution.

Clinical efficacy against specific pathogens

Susceptibility to Enterobacteriaceae

Ceftobiprole, like other cephalosporins is susceptible to hydrolysis that may be produced by Enterobacteriaceae including many of the extended spectrum beta lactamases (ESBLs), serine carbapenemases, class B metallo-beta-lactamases (among others). Therefore, information on the prevalence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) should be taken into consideration when selecting Zevtera for treatment (see *Pharmacodynamic Properties*).

Interference with serological testing

Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia

The development of a positive direct antiglobulin test may occur during treatment with a cephalosporin. In clinical studies there was no evidence of haemolytic anaemia. However, the possibility that haemolytic anaemia may occur in association with Zevtera treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zevtera should be investigated for this possibility.

Potential interference with serum creatinine test

It is not known whether ceftobiprole, like some other cephalosprins, interferes with the alkaline picrate assay to measure serum creatinine (Jaffé reaction), which may lead to erroneously high creatinine measurements. During treatment with Zevtera it is recommended that an enzymatic method of measuring serum creatinine be used.

Potential interference with urine glucose test

During treatment with Zevtera it is recommended that an enzymatic method to detect glucosuria be used, because of potential interference with tests using the copper reduction technique.

Appropriate use of antibiotics

Consideration should be given to official guidance on the appropriate use of antibiotics.

This medicinal product contains approximately 1.3 mmol (29 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Effects on Fertility

The effects of ceftobiprole medocaril sodium on fertility in humans have not been studied. Rat fertility was unaffected at IV doses of up to 360 mg/kg/day (3-times the anticipated clinical

exposure based on plasma concentration of ceftobiprole).

Use in Pregnancy – Category B1

There are no adequate and well-controlled studies with Zevtera in pregnant women. There was no evidence of teratogenicity in rats or monkeys administered Zevtera during the period of organogenesis at IV of approximately 3- and 6-times the anticipated clinical concentration, respectively. In rats administered Zevtera at 360 mg/kg/day IV from early gestation to weaning, there was a slight reduction in the numbers of live offspring, but pup development was normal.

As no data in exposed human pregnancies are available, Zevtera should not be used during pregnancy unless strictly necessary.

Use in lactation

Animal studies have shown the excretion of ceftobiprole/metabolites in milk. It is unknown whether ceftobiprole is excreted in human milk and the risk of diarrhoea and fungal infection of the mucous membranes in the breast-fed infant cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zevtera therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric use

The safety and efficacy of Zevtera in children aged birth to < 18 years have not yet been established. Zevtera is not recommended for use in children or adolescents below 18 years of age.

Use in the Elderly (>65 years)

No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment.

Genotoxicity

Ceftobiprole medocaril sodium and ceftobiprole were examined in a battery of *in vitro* and *in vivo* assays. Ceftobiprole medocaril sodium was negative in a bacterial and a mammalian cell mutation assay. In another mammalian cell mutation assay, ceftobiprole medocaril sodium exhibited mutagenic activity at cytotoxic concentrations and ceftobiprole induced an unequivocal effect at very high cytotoxic concentrations of >2500 ug/mL. In an *in vitro* human lymphocyte chromosomalaberration assay, ceftobiprole medocaril sodium, but not ceftobiprole, was clastogenic at cytotoxic concentrations. No genotoxic activity was seen in the mouse bone marrow micronucleus and rat hepatocyte unscheduled DNA synthesis *in vivo* assays. Ceftobiprole medocaril sodium is unlikely to be genotoxic in man.

Carcinogenicity

Because of the short-term duration of the clinical therapy and the low potential of ceftobiprole medocaril sodium for genotoxicity, carcinogenicity studies have not been conducted.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, since dizziness is a common undesirable effect, driving and using machines is not recommended while on treatment with Zevtera.

INTERACTIONS WITH OTHER MEDICINES

In vitro studies have been carried out to investigate potential interactions at the level of CYP enzymes. However, as the concentrations of ceftobiprole used in these studies were limited by solubility, the potential for CYP drug interactions cannot be ruled out.

In vitro studies showed that ceftobiprole inhibits OATP1B1 and OATP1B3 with IC_{50}s of 67.6 μM and 44.1 μM, respectively. Zevtera may increase concentrations of drugs eliminated by OATP1B1 and OATP1B3, such as statins (pitavastin, pravastatin, rosuvastatin), glyburide, and bosentan.

No clinical interaction studies have been performed. Caution is advised when Zevtera is administered together with drugs with narrow therapeutic index.

ADVERSE EFFECTS

Summary of the safety profile

In therapeutic clinical studies in community acquired pneumonia and hospital acquired pneumonia 696 subjects received Zevtera.

The most common adverse events occurring in ≥ 3% of patients treated with Zevtera in these 696 patients were diarrhoea, vomiting, hypokalaemia, nausea, hyponatraemia, pyrexia, headache, phlebitis, constipation, insomnia, rash, urinary tract infection, respiratory failure, hypotension, and anemia.,

Less frequently reported, but more serious adverse reactions include thrombocytopenia, leukopenia, anaphylactic shock, *Clostridium difficile* colitis, convulsion, agitation (including panic attacks and nightmares), and renal failure.

Table 6: Treatment emergent adverse events occurring in ≥2% of patients on Zevtera or comparator in studies in community acquired pneumonia and hospital acquired pneumonia)

Preferred term	Percentage of patients (%)	
	Zevtera **N=696**	**Linezolid/ceftazidime (HAP); ceftriaxone ± linezolid (CAP)** **N= 708**
Blood and lymphatic disorders		
Anaemia	21 (3.0 %)	31 (4.4 %)
Gastrointestinal disorders		
Nausea	45 (6.5 %)	26 (3.7 %)
Diarrhoea	65 (9.3 %)	87 (12.3 %)

Preferred term	Percentage of patients (%)	
	Zevtera N=696	Linezolid/ceftazidime (HAP); ceftriaxone ± linezolid (CAP) N= 708
Vomiting	55 (7.9 %)	21 (3.0 %)
Constipation	27 (3.9 %)	32 (4.5 %)
Abdominal pain	14 (2.0 %)	16 (2.3 %)
General disorders and administration site conditions		
Pyrexia	39 (5.6 %)	40 (5.6 %)
Oedema peripheral	15 (2.2 %)	22 (3.1 %)
Chest pain	11 (1.6 %)	14 (2.0 %)
Infections and infestations		
Urinary tract infection	22 (3.2 %)	15 (2.1 %)
Pneumonia	17 (2.4 %)	25 (3.5 %)
Sepsis	15 (2.2 %)	11 (1.6 %)
Investigations		
Alanine aminotransferase increased	13 (1.9 %)	18 (2.5 %)
Aspartate aminotransferase increased	11 (1.6 %)	16 (2.3 %)
Metabolism and nutrition disorders		
Hypokalaemia	51 (7.3 %)	51 (7.2 %)
Hyponatraemia	42 (6.0 %)	33 (4.7 %)
Hypoglycaemia	11 (1.6 %)	15 (2.1 %)
Hyperglycaemia	11 (1.6 %)	21 (3.0 %)
Nervous system disorders		
Headache	30 (4.3 %)	34 (4.8 %)
Dizziness	12 (1.7 %)	14 (2.0 %)
Psychiatric disorders		
Insomnia	26 (3.7 %)	23 (3.2 %)
Respiratory, thoracic, and mediastinal disorders		
Respiratory failure	22 (3.2%)	21 (3.0 %)
Bronchospasm	14 (2.0 %)	15 (2.1 %)
Pleural effusion	14 (2.0 %)	13 (1.8 %)
Skin and subcutaneous tissue disorders		
Rash	23 (3.3 %)	15 (2.1 %)
Decubitus ulcer	12 (1.7 %)	17 (2.4 %)
Vascular disorders		
Phlebitis	29 (4.2 %)	19 (2.7 %)
Hypertension	22 (3.2 %)	26 (3.7 %)
Hypotension	19 (2.7 %)	16 (2.3 %)

Table 7: Adverse drug reactions that were reported as related to Zevtera in <2% of patients during Phase 3 pneumonia studies

Frequency of adverse drug reaction	System organ class	Adverse drug reactiont
Uncommon (≥0.1 to <1%)		
	Nervous system disorder	Dysgeusia
Rare		

Frequency of adverse drug reaction	System organ class	Adverse drug reactiont
(≥0.01 to <0.1)		
	Blood and lymphatic system	Leukopenia, thrombocythaemia, leukocytosis, thrombocytopenia
	Cardiac disorders	Cardiac failure congestive, extrasystoles, arrhythmia, atrial fibrillation, cardiac arrest
	Congenital, familial, and genetic disorders	Colour blindness, epidermolysis
	Ear and labyrinth disorders	Vertigo, tinnitus
	Eye disorders	Visual disturbance
	Gastrointestinal disorders	Dyspepsia, abdominal distension, disbacteriosis, abdominal tenderness, dysphagia, gastroduodenitis, oesophagitis, toothache
	General disorders and administration site conditions	Infusion site pain, asthenia, feeling hot, malaise, chest discomfort, feeling jittery, generalised oedema, infusion site reaction, feeling cold, infusion site irritation, infusion site oedema, injection site pain, injection site phlebitis, oedema
	Hepatobiliary disorders	Hepatitis, liver disorder, cholestasis, hepatic function abnormal
	Immune system disorders	Hypersensitivity, anaphylactic shock
	Infections and infestations	Oral candidiasis, candidiasis, clostridial infection, Clostridium difficile colitis, bacteraemia, bronchopneumonia, fungal skin infection, lung abcess, oral herpes, otitis media, viral infection
	Investigations	Blood triglycerides increased, gamma-glutamyltransfrase increased, liver function test abnormal, blood lactate dehydrogenase increased, blood alkaline phosphatase increased, creatinine renal clearance decreased, hepatic enzyme increased, blood uric acid increased, blood chloride decreased, blood pressure increased, electrocardiogram QT prolonged, electrocardiogram T wave inversion, haemoglobin decreased, prothrombin time prolonged

Frequency of adverse drug reaction	System organ class	Adverse drug reactiont
	Metabolism and nutrition	Anorexia, decreased appetite, hypocalcaemia, fluid retention, hyperchloraemia, hyperkalaemia, hypernatraemia, hypervolaemia.
	Musculoskeletal and connective tissue disorders	Pain in extremity, muscle contracture
	Nervous system disorders	Coma, convulsion, paraesthesia, parosmia, hypotonia, tremor
	Psychiatric disorders	Agitation, delirium, euphoric mood, nightmare, panic attack
	Renal and urinary disorders	Polyuria, renal failure, ketonuria, nephrolithiasis, proteinuria, urinary retention
	Respiratory, thoracic, and mediastinal disorders	Cough, tachypnoea, pulmonary congestion, pulmonary oedema, rales, respiratory distress
	Skin and subcutaneous tissue disorders	Pruritus, urticaria, dermatitis allergic, hyperhidrosis, erythema, rash erythematous, rash vesicular, skin warm
	Vascular disorders	Flushing, shock, venous thrombosis

DOSAGE AND ADMINISTRATION

Zevtera must be reconstituted and then further diluted (see **Special precautions for disposal and other handling**) prior to administration by intravenous infusion over a period of 2 hours.

Adults (18 years and older)

The recommended dose of Zevtera is 666.6 mg administered as a 2-hour intravenous infusion every 8 hours. Treatment is continued for 4-14 days depending on disease severity and patient response. For CAP, a switch to an appropriate oral antibiotic may be considered after completion of at least 3 days of intravenous ceftobiprole medocaril sodium treatment, depending on the patient's clinical response.

Children (<18 years)

The safety and efficacy of Zevtera in children aged birth to < 18 years have not yet been established. Zevtera is not recommended for use in children or adolescents below 18 years of age.

Elderly

No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see below and *Pharmacokinetic Properties*).

Renal impairment

In patients with mild renal impairment (i.e., creatinine clearance [CL_{CR}] 50 to 80 mL/min), no dosage adjustment is necessary. The dose should be adjusted when creatinine clearance is ≤ 50 mL/min, as shown below.

Creatinine clearance (mL/min)	Dosage regimen	Frequency
50 - 80	666.6 mg (2-hour intravenous infusion)	every 8 hours
30 to < 50	666.6 mg (2-hour intravenous infusion)	every 12 hours
< 30	333.3 mg (2-hour intravenous infusion)	every 12 hours
End-stage renal disease requiring dialysis	333.3 mg with or without intermittent haemodialysis	every 24 hours

Ceftobiprole medocaril sodium is haemodialysable.
Due to limited clinical data and an expected increased exposure of Zevtera and its metabolite, Zevtera should be used with caution in patients with severe renal impairment.

Supra-normal creatinine clearance > 150 mL/min
At start of treatment the prescribing physician should assess the renal function of the patient based on creatinine clearance expressed in mL/minute.

In patients with a supra-normal creatinine clearance (> 150 mL/min), based on pharmacokinetic/pharmacodynamic considerations, prolongation of the infusion duration to 4 hours is recommended (see *Pharmacokinetic Properties*).

Hepatic impairment
There is no experience in patients with hepatic impairment. However, as ceftobiprole undergoes minimal hepatic metabolism and is eliminated predominantly by the kidneys, no dosage adjustment is considered necessary in patients with hepatic impairment.

Special precautions for disposal and other handling
The product is for single use in one patient only. Discard any residue.

Zevtera must be reconstituted and then further diluted prior to infusion. The recommended dose of 666.6 mg ceftobiprole medocaril sodium is administered in 250 mL of diluent. This has to be taken into consideration when treating patients with heart failure or other conditions. The fluid load may also affect the risk of hyponatraemia (see Adverse effects).

Step 1. Reconstitution

10 mL of sterile water for injections or dextrose 50 mg/mL (5%) solution for injection should be added to the vial and the vial should be shaken vigorously until complete dissolution, which in some cases may take up to 10 minutes. The volume of the resulting concentrate is approximately 10.6 mL. Any foam should be allowed to dissipate and the reconstituted solution should be inspected visually to ensure the product is in solution and particulate matter is absent. The reconstituted concentrate contains 66.7 mg/mL of ceftobiprole medocaril sodium and must be further diluted prior to administration. It is recommended that the reconstituted solution be further diluted immediately. However, if this is not possible the reconstituted solution can be stored at room temperature for up to one hour, or in a refrigerator for up to 24 hours.

Step 2. Dilution

Preparation of 666.6 mg dose of Zevtera solution for infusion

10 mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5-10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 666.6 mg dose of ceftobiprole medocaril sodium.

Preparation of 333.3 mg dose of Zevtera solution for infusion for patients with severe renal impairment

5 mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 125 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5-10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 333.3 mg dose of ceftobiprole medocaril sodium.

The solution for infusion should be clear to slightly opalescent and yellowish in colour. The solution for infusion should be inspected visually for particulate matter prior to administration, and discarded if particulate matter is visible.

Stability after reconstitution and dilution
After reconstitution
Chemical, and physical in-use stability of the reconstituted solution (66.7 mg/mL) has been demonstrated for 1 hour at 25°C and up to 24 hours at 2°C–8°C.

After dilution
To reduce microbiological hazard, use as soon as practicable after reconstitution/dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours or for not more than 6 hours at room temperature (including infusion time). If **Lactated Ringer's solution for injection** is used as diluent, do not refrigerate the infusion solution.

From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

The reconstituted and infusion solutions should not be frozen or exposed to direct sunlight.

If the infusion solution is stored in the refrigerator, it should be equilibrated to room temperature prior to administration. The infusion solution does not need to be protected from light during administration.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Incompatibilities with other medicines

This medicinal product must not be mixed with other medicinal products except those mentioned in *Special precautions for disposal and other handling.*

This medicinal product must not be mixed or administered simultaneously with calcium-containing solutions (except Lactated Ringer's solution for injection). See sections *Dosage and Administration, Precautions, Special precautions for disposal and other handling*.

This medicinal product should not be simultaneously administered via a Y site with: Acyclovir sodium, Amikacin sulphate, Amiodarone hydrochloride, Amphotericin B (colloidal), Calcium gluconate, Caspofungin acetate, Ciprofloxacin, Cisatracurium besylate, Diazepam, Diltiazem hydrochloride, Diphenhydramine hydrochloride, Dobutamine hydrochloride, Dopamine hydrochloride, Esomeprazole sodium, Famotidine, Filgrastim, Gentamicin sulphate, Haloperidol lactate, Hydromorphone hydrochloride, Hydroxyzine hydrochloride, Insulin human regular, Insulin lispro, Labetalol hydrochloride, Levofloxacin, Lidocaine hydrochloride, Magnesium sulphate, Meperidine hydrochloride, Metoclopramide hydrochloride, Midazolam hydrochloride, Milrinone lactate, Morphine sulphate, Moxifloxacin hydrochloride, Ondansetron hydrochloride, Pantoprazole sodium, Potassium phosphates, Promethazine hydrochloride, Remifentanil hydrochloride, Sodium phosphates, Tobramycin sulphate.

OVERDOSAGE

Information on overdosage with Zevtera in humans is not available. The highest total daily dose administered in Phase 1 trials was 4 g ceftobiprole medocaril sodium (1.3 g every 8 hours). If overdosage should occur, it should be treated symptomatically. Ceftobiprole plasma concentrations can be reduced by haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Zevtera vials contain 666.6 mg of ceftobiprole medocaril sodium (equivalent to 500.0 mg of ceftobiprole). After reconstitution, each mL of concentrate contains 66.7 mg of ceftobiprole medocaril sodium (equivalent to 50 mg of ceftobiprole). The medicinal product contains approximately 1.3 mmol (29 mg) sodium per dose.

Available as 10 x 20 mL clear type I glass vials fitted with a grey bromobutyl elastomeric closure and an aluminium seal with a blue plastic flip-off cap.

Storage

Store in a refrigerator (2°C–8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted and/or diluted medicinal product, see **DOSAGE AND ADMINSTRATION**.

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine - S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

10 November 2015

DATE OF MOST RECENT AMENDMENT

20 November 2015

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