Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adaluzis 500mg Powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of ceftobiprole (as 666.6 mg of ceftobiprole medocaril sodium). After reconstitution, each mL of concentrate contains 50 mg of ceftobiprole (as 66.7 mg of ceftobiprole medocaril sodium).

Excipient(s) with known effect:

Each vial contains approximately 1.3 mmol (29 mg) sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White, yellowish to slightly brownish, cake to broken cake or powder.

The pH of the reconstituted solution is between 4.5 and 5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zevtera is indicated for the treatment of the following infections in adults, term neonates, infants, children and adolescents (see sections 4.4 and 5.1):

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

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

4.2 Posology and method of administration

Posology
The recommended regimen for adult and paediatric patients with normal renal function is shown in Table 1.

Table 1 Dosage in adult and paediatric patients with normal renal function or mild renal impairment (i.e., creatinine clearance [CL_{CR}] ≥ 50 mL/min)

Age group	Body weight (kg)	Ceftobiprole dose	Concentration of infusion solution[a]	Infusion time/ Frequency
Adults	-	500 mg	2 mg/mL	2 h infusion / every 8 hours
Adolescents aged 12 to < 18 years	≥ 50 kg	500 mg		
	< 50 kg	10 mg/kg		

Infants aged ≥ 3 months and children < 12 years	≥ 33 kg	500 mg	4 mg/mL	2 h infusion / every 8 hours
	< 33 kg	15 mg/kg		
Term neonates and infants < 3 months	≥ 4 kg	15 mg/kg		2 h infusion / every 12 hours
	< 4 kg	10 mg/kg		

[a] See section 6.6.

For adult and paediatric patients aged ≥ 12 years, the ceftobiprole concentration of the infusion solution is 2 mg/mL. To limit the infusion volume for paediatric patients < 12 years of age, the ceftobiprole concentration of the infusion solution for these patients is 4 mg/mL.

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.

Paediatric population
The safety and efficacy of Zevtera in preterm neonates have not been established. Zevtera is not recommended for use in preterm neonates.

Special populations
Elderly patients
No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see below and section 5.2).

Renal impairment and end-stage renal disease requiring dialysis
In adult and paediatric patients with mild renal impairment (i.e., CL_{CR} 50 to 80 mL/min), no dosage adjustment is necessary.

In adult and paediatric patients with moderate renal impairment (CL_{CR} 30 to < 50 mL/min), adult and paediatric patients with severe renal impairment (CL_{CR} 10 mL/min to < 30 mL/min), and adult patients with end-stage renal disease (ESRD) requiring dialysis, the dosage of Zevtera should be adjusted as shown in Table 2. There is insufficient information to recommend dosage adjustments in paediatric patients with end-stage renal disease (ESRD).

Table 2 Dosage in adult and paediatric patients with moderate renal impairment (CL_{CR} 30 to <50 mL/min), severe renal impairment (CL_{CR} <30 mL/min), or patients with ESRD requiring dialysis

Age group	**Creatinine clearance, CL_{CR} (mL/min)[a]**	**Ceftobiprole dose**	**Concentration of infusion solution[d]**	**Infusion time (hours)/ Frequency**
Adults	30 to < 50	500 mg	2 mg/mL	2 h infusion / every 12 hours
	10 to < 30	250 mg		
	ESRD, including haemodialysis[b]	250 mg		2 h infusion / every 24 hours
Adolescents Aged 12 to < 18 years	30 to < 50	7.5 mg/kg		2 h infusion / every 12 hours
	10 to < 30	7.5 mg/kg[c]		
Children aged 6 to < 12 years	30 to < 50	7.5 mg/kg	4 mg/mL	2 h

				infusion / every 12 hours
	10 to < 30	7.5 mg/kg[c]		2 h infusion / every 24 hours
Infants aged ≥ 3 months and children < 6 years	30 to < 50	10 mg/kg		2 h infusion / every 12 hours
	10 to < 30	10 mg/kg		2 h infusion / every 24 hours
Term neonates and infants < 3 months, bodyweight ≥ 4 kg	30 to < 50	15 mg/kg		2 h infusion / every 12 hours
	10 to < 30	15 mg/kg		2 h infusion / every 24 hours
Term neonates and infants < 3 months, bodyweight < 4 kg	30 to < 50	10 mg/kg		2 h infusion / every 12 hours
	10 to < 30	10 mg/kg		2 h infusion / every 24 hours

Note: All regimen administered as a 2 h infusion with a maximum allowable dose of 500 mg regardless of patient's weight unless otherwise specified.
[a] Calculated in mL/min/1.73 m^2 using the Schwartz formula for paediatric patients. CL_{CR} should be closely monitored and the dose adjusted according to changing renal function.
[b] Ceftobiprole medocaril sodium is haemodialysable; thus Zevtera should be administered after haemodialysis on haemodialysis days.
[c] Up to a maximum dose of 250 mg.
[d] See section 6.6.

Dose recommendations for term neonates, infants, children, and adolescents are based on pharmacokinetic modelling. 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 (see section 5.2).

Patients with 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 section 5.2).

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.

Method of administration

Zevtera must be reconstituted and then further diluted (see section 6.6) prior to administration by intravenous infusion over a period of 2 hours.

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 sections 4.4, 6.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to the cephalosporin class of antibacterials.
Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions
As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported. In case of severe hypersensitivity reactions, treatment with Adaluzis 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 Adaluzis, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if Adaluzis is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Dosing above the recommended dose range
There is no clinical experience with Zevtera doses higher than the recommended 500 mg administered every eight hours.

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.

Clostridioides 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 section 4.8). Discontinuation of therapy with Zevtera and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

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 (see section 5.3). 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 section 6.2).

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 section 5.1). 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 section 5.1).

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 micromole and 44.1 micromole respectively. Adaluzis 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 Adaluzis is administered together with drugs with narrow therapeutic index.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies with Adaluzis in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

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

Breast-feeding
Animal studies have shown the excretion of ceftobiprole/metabolites in milk at low concentrations. 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 Adaluzis therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
The effects of ceftobiprole medocaril on fertility in humans have not been studied. Animal studies with ceftobiprole medocaril do not indicate harmful effects with respect to fertility.

4.7 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 Adaluzis.

4.8 Undesirable effects

Summary of the safety profile
In therapeutic clinical studies in adults, 1,668 subjects received Zevtera. Within these trials there were a total of 1,239 subjects (696 subjects in community-acquired pneumonia and nosocomial pneumonia, and 543 subjects in complicated skin and soft tissue infections, cSSTIs) who received 500 mg three times daily, 389 subjects (cSSTIs) who received 500 mg twice daily and 40 subjects (cSSTIs) who received 750 mg twice daily.

The most common adverse reactions occurring in ≥ 3% of patients treated with Zevtera were nausea, vomiting, diarrhoea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity) and dysgeusia.

Less frequently reported, but more serious, adverse reactions include thrombocytopenia, agranulocytosis, anaphylaxis, *Clostridioides difficile*, colitis, convulsion, agitation (including anxiety, panic attacks and nightmares), and renal failure.

Paediatric population
In one therapeutic clinical study in paediatric patients with community-acquired or nosocomial pneumonia, 94 subjects aged 3 months to 17 years received Zevtera. In two other clinical studies, 64 subjects aged 3 months to 17 years and 15 subjects aged 0 (birth) to < 3 months received a single dose of Zevtera. Overall, the safety profile in paediatric patients was similar to that observed in the adult population.

Tabulated list of adverse reactions
The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to very common (1/10); common (1/100 to < 1/10); uncommon (1/1,000 to < 1/100); rare (1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data):

Adverse reactions from clinical studies and post-marketing reports

System Organ Class	Frequency: adverse events
Infections and infestations	Common: Fungal infection (including vulvovaginal, oral and cutaneous fungal infections) Uncommon: *Clostridioides difficile* colitis(including pseudomembranous colitis)
Blood and lymphatic system disorders	Uncommon: Eosinophilia, leukopenia, anaemia, thrombocytosis, thrombocytopenia Not known: Agranulocytosis
Immune system disorders	Common: Hypersensitivity reactions (including urticaria, pruritic rash and drug hypersensitivity) Uncommon: Anaphylactic reactions
Metabolism and nutrition disorders	Common: Hyponatraemia Uncommon: Hypokalaemia
Psychiatric disorders	Uncommon: Insomnia, agitation (including anxiety, panic attacks and nightmares)

Nervous system disorders	Common: Dysgeusia, headache, dizziness, somnolence Uncommon: Convulsions (including seizure, epilepsy, generalized tonic-clonic seizure, myoclonic epilepsy, myoclonus, seizure like phenomena and status epilepticus)
Respiratory, thoracic and mediastinal disorders	Uncommon: Dyspnoea, pharyngolaryngeal pain, asthma
Gastrointestinal disorders	Common: Nausea, vomiting , diarrhoea, abdominal pain, dyspepsia
Hepatobiliary disorders	Common: Hepatic enzymes increased (including AST, ALT, LDH and alkaline phosphatase)
Skin and subcutaneous tissue disorders	Common: Rash (including macular, papular, maculo-papular and generalised rash), pruritus
Musculoskeletal and connective tissue disorders	Uncommon: Muscle spasms
Renal and urinary disorders	Uncommon: Renal failure (including potential interactions with nephrotoxic drugs)
General disorders and administration site conditions	Common: Infusion site reactions Uncommon: Peripheral oedema
Investigations	Uncommon: Blood triglycerides increased, blood creatinine increased, blood glucose increased Not known: Coombs Direct Test Positive

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace , IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Information on overdosage with Adaluzis in humans is not available. The highest total daily dose administered in Phase 1 trials was 3 g (1 g every 8 hours). If overdosage should occur, it should be treated symptomatically. Ceftobiprole plasma concentrations can be reduced by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cephalosporins, ATC code: J01DI01

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 mecA*LGA251). Ceftobiprole also binds to PBP2b in *Streptococcus pneumoniae* (penicillin-intermediate), PBP2x in *S. pneumoniae* (penicillin resistant), and to PBP5 in *Enterococcus faecalis*.

Mechanisms 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/mL)	
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.		

PK/PD 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 HAP (not including VAP) and CAP that were susceptible to ceftobiprole in vitro:

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

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

Data from clinical studies

Nosocomial pneumonia

Adaluzis demonstrated efficacy in a well-controlled randomised Phase 3 study in patients with HAP. Non-inferiority between Adaluzis and the comparator group could not be demonstrated in patients with VAP (i.e., patients who develop pneumonia > 48 hours after onset of ventilation). In VAP, clinical cure rates in Adaluzis treated patients were 37.7% in the Adaluzis group (20

out of 53 patients) compared to 55.9% in the ceftazidime plus linezolid group (33 out of 59 patients), see also sections 4.1 and 4.4.

5.2 Pharmacokinetic properties

Plasma concentrations
The mean pharmacokinetic parameters of Zevtera in healthy adults for a single 500 mg dose administered as a 2-hour infusion and multiple 500 mg doses administered every 8 hours as 2-hour infusions are summarised in Table 1 (see section 4.2). Pharmacokinetic characteristics were similar with single and multiple dose administration.

Mean (standard deviation) pharmacokinetic parameters of Zevtera in healthy adults

Parameter	Single 500 mg dose administered as a 120-minute infusion	Multiple 500 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 (L/h)	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 healthy adults.

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

Ceftobiprole undergoes minimal metabolism to the open-ring metabolite, which is microbiologically inactive. Systemic exposure of 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 PgP, 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 protein binding is low (16%) and is not a PgP 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 (see section 4.5).

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

Elimination
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 healthy adults, 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.

Pharmacokinetic/Pharmacodynamic Relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of Zevtera exceeds the minimum inhibitory concentration of the infecting organism (%T>MIC) has been shown to best correlate with efficacy in clinical and pre-clinical pharmacokinetic/pharmacodynamic studies.

Special Populations

Renal impairment

The estimation of creatinine clearance should be based on the Cockcroft-Gault formula using actual body weight in adult patients and the Schwartz formula in paediatric patients. During treatment with ceftobiprole it is recommended that an enzymatic method of measuring serum creatinine be used (see section 4.4).

The pharmacokinetics of ceftobiprole are similar in healthy adults 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 adults with normal renal function.

Dosage adjustment is recommended in patients with moderate to severe renal impairment (see section 4.2). Dose recommendations for term neonates, infants, children, and adolescents are based on pharmacokinetic modelling.

End-stage renal disease requiring dialysis

AUCs of ceftobiprole and of the microbiologically inactive ring-opened metabolite are substantially increased in adult patients with end-stage renal disease who require haemodialysis compared with healthy adults. In a study where six adult subjects with end-stage renal disease on haemodialysis received a single dose of 250 mg Zevtera by intravenous infusion, ceftobiprole was demonstrated to be haemodialysable with an extraction ratio of 0.7 (see section 4.2).

There is insufficient information to recommend dosage adjustment in paediatric patients with CL_{CR} < 10 mL/min/1.73 m^2 or end-stage renal disease requiring dialysis.

Patients with creatinine clearance > 150mL/min

Ceftobiprole systemic clearance (CL_{SS}) was 40% greater in adult 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 (see section 4.2).

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 (see section 4.2).

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 (see section 4.2).

Paediatric population

Population pharmacokinetic data showed that glomerular filtration rate maturation has an effect on the pharmacokinetics of ceftobiprole in paediatric patients aged 1 year and younger. Dose adjustments are required for term neonates, infants, children, and adolescents with body weight < 50 kg (see section 4.2).

Plasma concentrations in paediatric population

The mean exposures to Zevtera in paediatric subjects with normal renal function based on population PK modelling are summarised below (see section 4.2) and are similar to the mean exposures observed in adults.

Mean (standard deviation) pharmacokinetic parameters of Zevtera in paediatric subjects predicted from population PK modelling

Age group	Dosing regimen	Cmax (µg/mL)	AUC (h.µg/mL)
Birth to <3 months	15 mg/kg q12h[a]	31.1 (7.05)	298 (66.4)
3 month to <2 years	15 mg/kg q8h	30.3 (5.32)	278 (69.9)
2 to <6 years	15 mg/kg q8h	30.8 (4.98)	266 (55.3)
6 to <12 years	15 mg/kg q8h	35.2 (5.94)	312 (68.7)
12 to <18 years	10 mg/kg q8h	26.6 (4.92)	245 (56.9)

Adults	500 mg q8h	33.0 (4.83)	306 (35.7)

a - Patients with a body weight < 4 kg given 10 mg/kg q12h as a 2-h infusion.

Gender
Systemic exposure to ceftobiprole was higher in adult females than adult 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 adults 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.

5.3 Preclinical safety data

Reversible renal toxicity in the distal tubules due to precipitation of drug-like material was observed at high doses only in small animals such as rats and marmosets and after bolus administration. Absence of kidney toxicity was observed in animals at urinary concentrations up to 12 times higher than those observed in humans at the therapeutic dose. Convulsions were observed after both single and multiple doses at exposures of six times the human exposure and higher, based on C_{max}.

Infusion-site irritation leading to thrombus formation was observed in small animals (rats and marmosets) but not in dogs. In a pre- and post-natal development study in rats, litter size and survival up to 4 days postpartum were decreased at maternally toxic doses. The relevance of all these findings for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

This medicinal product must not be mixed or administered simultaneously with calcium-containing solutions (except Lactated Ringer's solution for injection). See sections 4.2, 4.4, 6.6.

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.

6.3 Shelf life

Powder vial
4 years

After reconstitution
Chemical, and physical in-use stability of the **reconstituted solution** (50 mg/mL) has been demonstrated for 1 hour at 25°C and up to 24 hours at 2°C–8°C.

After dilution
Chemical and physical in-use stability data support the total times for reconstitution and infusion of 2 mg/mL or 4 mg/mL ceftobiprole dilution solutions and are described in the tables below:

Use in adults and adolescents ≥ 12 years (2 mg/mL ceftobiprole): Total time by which reconstitution and infusion (including the period of infusion, see section 4.2) must be completed

Reconstitution solution diluent	**Infusion solution diluent**	**Infusion solutions stored at 25°C**		**Infusion solutions stored at 2°C to 8°C**
		Protected from light	NOT protected from light	Protected from light
Dextrose 50 mg/mL (5%) solution for injection or Water for injection	Sodium chloride 9 mg/mL (0.9%) solution for injection	24 hours	8 hours	96 hours
	Dextrose 50 mg/mL (5%) solution for injection	12 hours	8 hours	96 hours
	Lactated Ringer's solution for injection	24 hours	8 hours	Do not refrigerate

Use in children, infants, and neonates (< 12 years) (4 mg/mL ceftobiprole): Total time by which reconstitution and infusion (including the period of infusion, see section 4.2) must be completed

Reconstitution solution diluent	**Infusion solution diluent**	**Infusion solutions stored at 25°C**	**Infusion solutions stored at 2°C to 8°C**
		NOT protected from light	Protected from light
Dextrose 50 mg/mL (5%) solution for injection	Dextrose 50 mg/mL (5%) solution for injection	12 hours	24 hours
Water for injection	Sodium chloride 9 mg/mL (0.9%) solution for injection	8 hours	8 hours

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.

The infusion solution should be prepared and used as defined in section 6.6.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). 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 section 6.3.

6.5 Nature and contents of container

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

Pack size: 10 vials.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Zevtera must be reconstituted and then further diluted prior to infusion.

Step 1. Reconstitution

For adult and paediatric patients ≥ 12 years who require an infusion solution with a ceftobiprole concentration of 2 mg/mL, the lyophilized powder should be reconstituted with 10 mL of sterile water for injections or dextrose 50 mg/mL (5%) solution for injection.

For paediatric patients < 12 years who require an infusion solution with a ceftobiprole concentration of 4 mg/mL, the lyophilized powder must be reconstituted either with 10 mL dextrose 50 mg/mL (5%) solution for injection if further dilution with the same diluent solution (i.e., dextrose 50 mg/mL (5%) solution for injection) is used, or with 10 mL of water for injection if further dilution with sodium chloride 9 mg/mL (0.9%) solution for injection is used (see section 6.3 tables).

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 50 mg/mL of ceftobiprole (as 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 1 hour, or in a refrigerator for up to 24 hours.

Step 2. Dilution (infusion solution)

Use in adult and paediatric patients ≥ 12 years
Preparation of 500 mg dose of Zevtera solution for infusion (2 mg/mL ceftobiprole)
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.

In adults, the entire contents of the infusion bag should be infused to administer a 500 mg dose of Zevtera.

In paediatric patients ≥ 12 years, the volume to be administered is equivalent to the calculated dose in mg/kg but not exceeding a maximum of 500 mg of Zevtera (see section 4.2).

Preparation of 250 mg dose of Zevtera solution for infusion for adult 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 250 mg dose of Zevtera.

Use in paediatric patients < 12 years

Preparation of Zevtera solution for infusion at a concentration of 4 mg/mL of ceftobiprole

Administration via infusion bags, bottles or syringes:

The reconstituted solution prepared with 10 mL dextrose 50 mg/mL (5%) solution for injection must be diluted with the same diluent solution (i.e., dextrose 50 mg/mL (5%) solution for injection). The reconstituted solution prepared with 10 mL water for injection solution must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection.

10 mL should be withdrawn from an infusion container (e.g., PVC or PE infusion bags, glass bottles) containing 125 mL of diluent solution and replaced with 10 mL of the reconstituted solution withdrawn from the vial. The infusion solution should be gently inverted 5–10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The volume to be administered is equivalent to the calculated dose in mg/kg but not exceeding a maximum of 500 mg of Zevtera (see section 4.2).

For administration via a 50 mL syringe if the calculated dose does not exceed 200 mg, 4 mL of the reconstituted solution (equivalent to 200 mg ceftobiprole) prepared with dextrose 50 mg/mL (5%) solution for injection or water for injection should be withdrawn from the vial and diluted with 46 mL of the appropriate infusion solution diluent (see section 6.3). The infusion solution should be gently inverted 5–10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The volume to be administered is equivalent to the calculated dose in mg/kg but not exceeding a maximum of 500 mg of Zevtera (see section 4.2).

Appearance of diluted solution

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.

Detailed information on the time by which reconstitution, dilution and infusion must complete is provided in section 6.3.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Correvio
15 Rue du Bicentenaire
92800 Puteaux
France

8 MARKETING AUTHORISATION NUMBER

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