PRODUCT MONOGRAPH

^{Pr}ZEFTERA*

ceftobiprole medocaril for Injection

Sterile, lyophilized powder for Intravenous Infusion

500 mg/vial ceftobiprole as ceftobiprole medocaril

Antibacterial Agent

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Antibacterial Agent

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Sterile, lyophilized powder / 500 mg per vial ceftobiprole as ceftobiprole medocaril	None. *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

ZEFTERA (ceftobiprole medocaril for injection, henceforth known as ceftobiprole) is a cephalosporin antibiotic indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms in patients 18 years of age and older:

- Complicated skin and skin structure infections (cSSSI), including non-limb threatening diabetic foot infections without concomitant osteomyelitis caused by: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus* (including methicillin-resistant isolates), and *Streptococcus pyogenes* (see **DOSAGE AND ADMINISTRATION)**.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZEFTERA and other antibacterial drugs, ZEFTERA should be used only to treat or prevent infections that are proven or suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ceftobiprole. Empiric therapy with ZEFTERA may be initiated before the results of these tests are known. Once these results are available, antimicrobial therapy should be adjusted (see **DOSAGE AND ADMINISTRATION**).

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with significant differences in safety or effectiveness (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**). Population pharmacokinetic data showed there is no independent effect of age on the pharmacokinetics of ceftobiprole. Dosage adjustment is not required in elderly patients with normal renal function (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

Pediatrics (<18 years of age): No data available (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)**.

CONTRAINDICATIONS

ZEFTERA is contraindicated in patients with known serious hypersensitivity to ceftobiprole, any of the excipients, other cephalosporins, or in patients who have demonstrated anaphylaxis to ß-lactam antibiotics.

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving ß-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Anaphylaxis, including anaphylactic shock, has been observed with ZEFTERA. Before therapy with ZEFTERA is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other cephalosporins, penicillins or other allergens. **SERIOUS ACUTE HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS REQUIRE EMERGENCY TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES** (see Hypersensitivity Reactions).

General

As with other antibiotics, prolonged use of ZEFTERA may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if evidence of super-infection occurs during therapy.

Patients with necrotizing fasciitis, gas gangrene, eczema, neutropenia, neoplasia, and immuno-compromised patients, were not enrolled in these studies, therefore ZEFTERA is not recommended for use in treating such patients.

The every 12-hour dosing regimen has not been studied in patients with diabetic foot infections (see **DOSAGE AND ADMINISTRATION**).

Hyponatremia was observed in clinical trials with ZEFTERA. For patients at risk of hyponatremia, consideration should be given to the choice of infusion solution for ZEFTERA (see **DOSAGE AND ADMINISTRATION**).

Neurologic

Neuropathy

As with other beta-lactams, patients may experience seizures during treatment with ZEFTERA. Seizures associated with ZEFTERA have occurred most commonly in patients with pre-existing CNS/seizure disorders; therefore caution is advised when treating these patients.

Immune System

Hypersensitivity Reactions

SERIOUS ACUTE HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS REQUIRE EMERGENCY TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

If an allergic reaction to ZEFTERA occurs, discontinue the drug.

Infusion Site

Infusion site reactions, including pain and phlebitis, have been observed in clinical trials (see **ADVERSE DRUG REACTIONS**).

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ZEFTERA. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Renal
In patients with moderately or severely impaired renal function (CrCl 10 to < 50 mL/min), dosage adjustment is required (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**). Due to limited clinical data and an expected increased exposure of ceftobiprole and its metabolite, ZEFTERA should be used with caution in patients with severe renal impairment. The concomitant administration of aminoglycosides and some cephalosporins has caused nephrotoxicity. Concomitant administration of ZEFTERA with known nephrotoxic agents has not been studied.

ZEFTERA is not recommended for patients with end stage renal disease (CrCl < 10 mL/min) or in patients on any type of dialysis (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**). Ceftobiprole is hemodialyzable; however, there is insufficient information to make dose recommendations.

Special Populations
Pregnant Women: No clinical studies have been performed in pregnant women. ZEFTERA should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus. Reproductive studies in animals at doses up to two and eight times the human dose have not revealed any evidence of impaired fertility or harm to the fetus. Animal reproduction studies are not always predictive of a human response (see **PART II: SCIENTIFIC INFORMATION, TOXICOLOGY).**

Nursing Women: It is not known whether ceftobiprole is excreted in human breast milk. Breastfeeding should be discontinued during treatment with ZEFTERA. Studies in animals have shown that the concentration of ceftobiprole excreted in animal milk is ~20% of the maternal plasma levels (see **PART II: SCIENTIFIC INFORMATION, TOXICOLOGY).**

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients below the age of 18 have not been established. Therefore, use in patients under 18 years of age is not recommended.

Geriatrics (> 65 years of age): Of the total number of subjects in clinical studies treated with ZEFTERA, 22% were 65 and over, while 6% were 75 and over.

Dosage adjustment is not required in elderly patients with normal renal function (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**). Since elderly patients may have impaired renal function, creatinine clearance should be taken into consideration when determining dose in elderly patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse drug reactions in patients treated with ZEFTERA are: nausea (9.1%), dysgeusia (5.6%), vomiting (4.8%), diarrhea (4.8%), and headache (4.5%) The majority (92.6%) of adverse events were reported as mild to moderate in severity. Ceftobiprole was discontinued due to an adverse event in 3.8% of subjects compared with 4.1% for all comparators. During clinical trials, adverse drug reactions that led to ZEFTERA discontinuation were rash (0.6%),

nausea (0.5%), vomiting (0.4), hypersensitivity reactions (0.3%), and hyponatremia (0.3%). For comparators, adverse drug reactions leading to discontinuation were rash (0.9%), hypersensitivity reactions (0.9%), nausea (0.5%), infusion site reactions (0.5%) and diarrhea (0.5%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of other drugs and may not reflect rates observed in practice.

The safety of ZEFTERA in patients with complicated skin and skin structure infections (including patients with diabetic foot infections without concomitant osteomyelitis) was evaluated in two Phase 3 double-blind, active controlled trials involving 1,593 adult patients (932 of whom received ZEFTERA). All study treatments were administered for 7 to 14 days. Adverse drug reactions due to ZEFTERA 500 mg administered every 8 or 12 hours as a 120 or 60-minute infusion that occurred at a rate ≥ 1 % (as judged by investigator to be remotely, possibly or probably related to ZEFTERA) are listed in Table 1.

Table 1: Adverse Drug Reactions (%) Observed in Two Phase 3 Clinical Trials Occurring at a Rate ≥ 1%

Body System or Organ Class Preferred Term	Ceftobiprole N = 932 (%)	Comparator[1] N =661 (%)
Gastrointestinal disorders		
Nausea	9.1	5.3
Diarrhea	4.8	3.5
Vomiting	4.8	3.3
Constipation	1.2	2.0
Dyspepsia	1.1	0.6
Nervous system disorders		
Dysgeusia	5.6	0.9
Headache	4.5	2.4
Dizziness	2.7	0.8
General disorders and administration site conditions		
Pyrexia	1.3	0.9
Fatigue	1.1	0.9
Chills	1.0	0.6
Skin and subcutaneous tissue disorders		
Rash	2.7	2.6
Pruritus	1.7	4.7
Investigations		
Alanine aminotransferase increased	1.6	2.0
Aspartate aminotransferase increased	1.3	1.2
Vascular disorders		
Phlebitis	1.9	0.8
Metabolism and nutrition disorders		
Hyponatremia	1.1	0

[1] Vancomycin in the study that enrolled patients with gram-positive infections; vancomycin plus ceftazidime in the study that enrolled patients with gram-positive and gram-negative infections

The majority of cases of nausea were mild, self-limited and did not lead to discontinuation of ZEFTERA. Nausea occurred at a lower frequency in those patients who received a 120-minute infusion (7%) compared with patients who received a 60-minute infusion (12%).

Anaphylaxis, including anaphylactic shock, *Clostridium difficile* colitis and seizures were adverse drug reactions that occurred at a rate of less than 1% in these clinical trials.

There is limited experience in patients receiving more than 14 days of therapy (N= 18). The adverse events profile of subjects who received greater than 14 days of therapy was similar to the adverse event profile of subjects who received 14 days or less of therapy (see **PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS**).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse drug reactions that were possibly or probably related to ZEFTERA with an incidence of <1.0% and >0.3% in Phase 3 clinical studies were:

Blood and lymphatic system: anemia

Gastrointestinal: abdominal pain, dyspepsia, stomach discomfort, dry mouth

General disorders & administration site conditions: asthenia, chills, fatigue, peripheral oedema, pyrexia, infusion site pain, catheter site phlebitis, feeling hot

Infections and Infestations: vulvovaginal mycotic infection, fungal infection

Immune System Disorders: hypersensitivity

Investigations: blood creatinine increased, blood lactate dehydrogenase increased, eosinophil count increased, gamma-glutamyltransferase increased, liver function test abnormal, platelet count increased, decreased creatinine clearance, increase blood triglycerides, increased basophils, increased blood triglycerides

Metabolism and nutrition: hyperglycaemia

Musculoskeletal and connective tissue: muscle spasms, back pain, pain in extremity

Nervous system: somnolence

Psychiatric: agitation, insomnia, anxiety

Renal and urinary: urine odour abnormal, pollakiuria

Respiratory, thoracic and mediastinal: dyspnoea, pharyngeal pain

Skin and subcutaneous tissue: dermatitis allergic, hyperhidrosis, erythema, rash maculopapular, urticaria

Vascular: hot flush, thrombophlebitis, hypertension

Abnormal Hematologic and Clinical Chemistry Findings

See Table 1 and **Less Common Clinical Trial Adverse Drug Reactions (<1%).**

DRUG INTERACTIONS

Overview

In vitro induction studies were conducted with ceftobiprole at 5μM. The anticipated maximal plasma concentration of ceftobiprole in humans administered 500 mg of ceftobiprole q8h over 2 hour infusion is approximately 65μM. The studies demonstrated minimal inhibition and no induction potential with CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The potential of ceftobiprole to affect the CYP450 dependent metabolic clearance of co-administered drugs is low on the basis of these studies, and because the distribution of ceftobiprole is restricted to the extracellular compartment. The potential for other drugs to interact with ceftobiprole is minimal since only a small fraction of ceftobiprole is metabolized. Therefore, no relevant metabolic drug-drug interactions are anticipated.

In vitro experiments were conducted to determine whether ceftobiprole is a substrate or inhibitor for the drug (efflux) transporter P-gp. Ceftobiprole was not found to be a P-gp substrate or inhibitor.

When using specific catalyzed cytochrome-P450 (CYP450) reactions in human microsomes, ceftobiprole showed no significant inhibition of the tacrine 1- and 7-hydroxylation (CYP1A2), diclofenac 4'-hydroxylation (CYP2C9), *S*-mephenytoin 4'-hydroxylation (CYP2C19), bufuralol

1'-hydroxylation (CYP2D6), and testosterone 6-β-hydroxylation (CYP3A4); only a slight (8% to 28%) inhibitory potential was apparent in the highest concentration range tested (50 to 100 μM). In another experiment using cultured human hepatocytes, 5 μM ceftobiprole caused no induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4/5.

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

Drug-Drug Interactions

Clinical drug-drug interaction studies have not been performed. Population pharmacokinetic analyses failed to demonstrate an effect of the following concomitant medications on the pharmacokinetics of ceftobiprole: fentanyl, lidocaine, acetaminophen, diclofenac, acetylsalicylic acid, heparin, diphenhydramine, propofol, hydromorphone hydrochloride, methadone, hydrocodone bitartrate, metamizole sodium, furosemide.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

On the basis of pharmacokinetic data in patients with moderate to severe renal impairment, the dose of ZEFTERA should be adjusted (see **Recommended Dose and Dosage Adjustment**, **Patients with Renal Impairment**).

Recommended Dose and Dosage Adjustment

Infection	Pathogens	Recommended Dose	Intravenous Infusion	Treatment Duration
Complicated Skin and Skin Structure Infections without Diabetic Foot Infections	**Gram positive only*** - *Staphylococcus aureus* (including methicillin-resistant) - *Streptococcus pyogenes*	500 mg every 12 hours	60 minutes	7-14 days
	Gram negative only *Escherichia coli* *Proteus mirabilis* *Enterobacter cloacae* *Klebsiella pneumoniae* **Gram negative and Gram positive**	500 mg every 8 hours	120 minutes	7-14 days
Complicated Skin and Skin Structure Infections with Diabetic Foot Infections (non Limb Threatening without concomitant Osteomyelitis) **	**Gram positive** - *Staphylococcus aureus* (including methicillin-resistant) **Gram negative** *Escherichia coli* *Proteus mirabilis* *Enterobacter cloacae* *Klebsiella pneumoniae* **Gram negative with or without Gram positive**	500 mg every 8 hours	120 minutes	7-14 days

* In documented cases of Gram positive infection only
** The every 12-hour dosing regimen has not been studied in patients with diabetic foot infections and therefore is not recommended in these patients. (See **WARNINGS and PRECAUTIONS)**.

Patients with Renal Impairment

In patients with mild renal impairment (i.e. creatinine clearance (CrCl) 50 to 80 mL/min), no dosage adjustment is necessary. In patients with moderate renal impairment (CrCl 30 to < 50 mL/min), the dosage of ZEFTERA should be 500 mg administered every 12 hours as a 120-minute intravenous infusion. In patients with severe renal impairment (CrCl < 30 mL/min), the dosage of ZEFTERA should be 250 mg administered every 12 hours as a 120-minute intravenous infusion (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency)**. Due to limited clinical data and an expected increased exposure of ceftobiprole and its metabolite, ZEFTERA should be used with caution in patients with severe renal impairment. ZEFTERA is not recommended for patients with end stage renal disease (CrCL<10mL/min) or in patients on any type of dialysis (see **WARNINGS AND PRECAUTIONS**, **Renal**). There is insufficient information to make dose recommendations.

The following formula may be used to estimate CrCl. The serum creatinine used in the formula should represent a steady state of renal function.

Males: Creatinine clearance (mL/min) = $\frac{\text{weight (kg) x (140 - age in years)}}{\text{72 x serum creatinine (mg/dL)}}$

Females: Creatinine clearance (mL/min) = 0.85 x value calculated for males

Patients with Hepatic Impairment

There is no experience in patients with hepatic impairment. However, as ceftobiprole undergoes minimal hepatic metabolism and is eliminated predominantly by the kidney, no dosage adjustment is necessary in patients with hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Other

No dosage adjustment is recommended solely based on age (18 years of age and older), gender or race (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions)**.

Administration

ZEFTERA is to be reconstituted and then further diluted prior to administration by intravenous infusion over a period of one or two hours.

Each vial is for single use only.

Reconstitution:

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
20 mL	10 mL	10.6 mL	50 mg/mL

The lyophilized powder should only be reconstituted with 10 mL water for injection or 5% dextrose solution for injection. The vial should be vigorously shaken. Complete dissolution may take up to 10 minutes. Before dilution into the infusion solution, any foam should be allowed to dissipate.

Dilution:

10 mL of the reconstituted solution should be removed from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 250 mL of 0.9% sodium chloride, 5% dextrose injection, or Lactated Ringer's injection infusion solution. The infusion solution should be gently inverted 5-10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. For detailed infusion solution storage conditions and stability, please see **STORAGE AND STABILITY**.

For patients with severe renal impairment (see **Recommended Dose and Dosage Adjustment**, **Patients with Renal Impairment)**, 5 mL of the reconstituted solution should be diluted into 125

mL of 0.9% sodium chloride, 5% dextrose injection or Lactated Ringer's injection infusion solution.

The infusion solution should be inspected visually for particulate matter prior to administration, and discarded if particulate matter is visible.

Compatibility
The compatibility of ZEFTERA with other drugs has not been established. ZEFTERA should not be mixed with or physically added to solutions containing other drugs.

OVERDOSAGE

Information on overdosage with ZEFTERA 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, a prototypical cephalosporin with bactericidal activity against a broad spectrum of gram-positive bacteria, including methicillin-resistant *Staphylococcus* species. Ceftobiprole is also active against many gram-negative bacteria, including many Enterobacteriaceae.

Mechanism of Action
Ceftobiprole has a bactericidal mode of action that involves tight binding to many common essential penicillin-binding proteins (PBPs) in both gram-positive and gram-negative bacteria.

Ceftobiprole has distinctive bactericidal activity against methicillin-resistant staphylococci primarily due to its novel strong binding to the staphylococcal PBP2a, the PBP that is chiefly responsible for ß-lactam resistance in methicillin-resistant staphylococci including methicillin-resistant *S. aureus* (MRSA).

Mechanism of resistance
Ceftobiprole is resistant to hydrolysis by *S. aureus* penicillinases, and is resistant to hydrolysis by many class C and class A ß-lactamases found in gram-negative bacteria. Like most cephalosporins, ceftobiprole is hydrolyzed by extended spectrum ß-lactamases (ESBLs), serine carbapenemases and metallo ß-lactamases.

Cross-resistance

Resistance to ceftobiprole due to spontaneous mutation in vitro is a rare occurrence. Although cross-resistance has been observed between ceftobiprole and some other advanced generation cephalosporins, some microorganisms resistant to other cephalosporins may be susceptible to ceftobiprole.

Pharmacodynamics

The effect of ceftobiprole on healthy subjects was evaluated in a QT/QTc study. Ceftobiprole had no effect on heart rate or other ECG parameters in healthy adults after administration of single intravenous therapeutic and supratherapeutic doses (see **PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY**).

Convulsions were observed after direct administration into the brain in mice and may be attributed to inhibition of GABA receptor-mediated neurotransmission (see **DETAILED PHARMACOLOGY, Animal Pharmacology**).

Pharmacokinetics

The mean pharmacokinetic parameters of ceftobiprole in adults for a single 500 mg dose administered as a 60-minute infusion and multiple 500 mg doses administered every 8 hours as 120-minute infusions are summarized in Table 2. Pharmacokinetic characteristics were similar with single and multiple dose administration.

Table 2: Mean (Standard Deviation) pharmacokinetic parameters of ceftobiprole in adults

Parameter	Single 500 mg dose administered as a 60 minute infusion	Multiple 500 mg doses administered every 8 hours as 120 minute infusions
C_{max} (μg/mL)	34.2 (6.05)	33.0 (4.83)
AUC (μg•h/mL)	116 (20.2)	102 (11.9)
$t_{1/2}$ (hours)	2.85 (0.55)	3.3 (0.3)
CL (L/h)	4.46 (0.84)	4.98 (0.58)

Ceftobiprole exhibits linear and time-independent pharmacokinetics. The Cmax and AUC of ceftobiprole increase in proportion to dose over a range of 125 mg to 1 g. Steady-state drug concentrations are attained on the first day of dosing; no appreciable accumulation occurs with q8h and q12h dosing in subjects with normal renal function (see **PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY**).

Absorption: ZEFTERA is administered intravenously and therefore has 100% bioavailability.

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

Metabolism: Conversion from the prodrug ceftobiprole medocaril, to the active moiety ceftobiprole, occurs rapidly and is mediated by plasma esterases. Prodrug concentrations are negligible and are measurable in plasma and urine only during infusion.

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.

Excretion: Ceftobiprole is eliminated primarily unchanged by renal excretion and the predominant mechanism responsible for elimination is glomerular filtration, with some active reabsorption. In preclinical studies, probenecid did not affect the pharmacokinetics of ceftobiprole, thereby indicating no involvement of active tubular secretion mechanisms. Elimination half-life of the open-ring metabolite was slightly longer, approximately 5 hours compared with ceftobiprole, which was approximately 3 hours. Following single dose administration, approximately 89% of the administered dose is recovered in the urine as active ceftobiprole (83%), the open-ring metabolite (5%) and ceftobiprole medocaril (<1%).

Special Populations and Conditions

Pediatrics: The pharmacokinetics of ceftobiprole have not been established in patients under 18 years of age.

Geriatrics: Population pharmacokinetic data showed there is no independent effect of age on the pharmacokinetics of ceftobiprole. Dosage adjustment is not required in elderly patients with normal renal function (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

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

Race: Population pharmacokinetic analyses (including Caucasians and a limited number of African-Americans and Other groups) showed no effect of race on the pharmacokinetics of ceftobiprole. Therefore, dosage adjustments based on race are not required.

Hepatic Insufficiency: The pharmacokinetics of ceftobiprole in patients with hepatic impairment have not been established. As ceftobiprole does not appear to undergo significant hepatic metabolism, the systemic clearance of ceftobiprole is not expected to be significantly affected by hepatic impairment. Due to the low protein binding of ceftobiprole, differences in albumin concentrations associated with hepatic impairment are not expected to significantly affect the free fraction of ceftobiprole. Therefore, dosage adjustments are not indicated for patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**, **Patients with Hepatic Impairment**).

Renal Insufficiency: The pharmacokinetics of ceftobiprole is similar in healthy volunteers and patients with mild renal impairment (CrCl > 50 to ≤ 80 mL/min). Ceftobiprole AUC was 2.5- and 3.5-fold higher in patients with moderate (CrCl ≥ 30 to ≤ 50 mL/min) and severe (CrCl < 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 (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

AUCs of ceftobiprole and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require hemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease on hemodialysis received a single dose of 250 mg ceftobiprole by intravenous infusion, the amount of ceftobiprole removed during the four-hour hemodialysis session was 70 mg (28% of the dose).

PK/PD Humans

A two-hour infusion administered every eight hours increases the T>MIC for both gram-positive and gram-negative pathogens. A one-hour infusion administered every 12 hours provides sufficient T>MIC for documented gram-positive infections (see **PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY**).

STORAGE AND STABILITY

Storage of Vials:

ZEFTERA vials should be stored refrigerated at 2-8°C in the carton in order to protect from light prior to constitution.

Storage of the Reconstituted and Infusion Solutions:

Chemical, physical and microbiological in-use stability data support the total times for reconstitution, dilution and infusion described in the table below:

Reconstitution Diluent (10 mL)	Max. shelf life of reconstituted solution		Infusion Solution Diluent (250 mL)	**Total Time** by which reconstitution, dilution and infusion must be completed		
	Reconstituted solution stored at 25°C	Reconstituted solution stored at 2-8°C (refrigerator)		Infusion solutions stored at 25°C		Infusion solutions stored at 2-8°C (refrigerator)
	Protected from light	Protected from light		Protected from light	NOT protected from light	Protected from light
Water for Injection or 5% Dextrose	1 hr	24 hr	0.9% sodium chloride	24 hr	8 hr	96 hr
			5% dextrose	12 hr	8 hr	96 hr
			Lactated Ringer's	24 hr	8 hr	Do not refrigerate

The reconstituted and infusion solutions should not be frozen. The reconstituted and infusion solutions should not be 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.

Please refer to **DOSAGE AND ADMINISTRATION**, **Administration** for method of preparation.

Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

Each vial is for single use only.

ZEFTERA must be reconstituted and then further diluted prior to infusion (see **DOSAGE AND ADMINISTRATION, Administration**).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZEFTERA is supplied as sterile single use clear 20 mL glass vials containing 500 mg ceftobiprole lyophilized powder (as 666.6 mg of ceftobiprole medocaril).

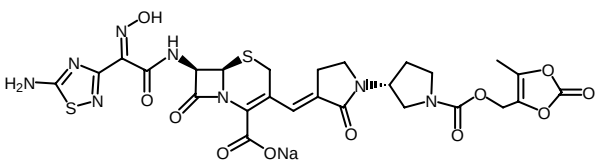
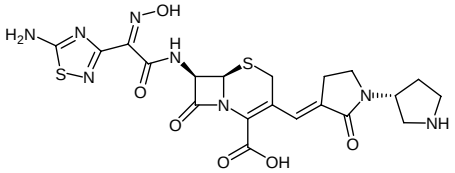
Supplied as 10 vials per carton.

ZEFTERA contains the following inactive ingredients: citric acid monohydrate, sodium hydroxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name	Ceftobiprole medocaril (prodrug)	Ceftobiprole (active moiety)
Chemical name	(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	(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino) acetyl]amino]-8-oxo-3-[(*E*)-[(3'*R*)-2-oxo-1,3'-bipyrrolidin-3-ylidene] methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
Molecular formula	$C_{26}H_{25}N_8NaO_{11}S_2$	$C_{20}H_{22}N_8O_6S_2$
Molecular mass	712.64	534.27
Structural formula		

Physicochemical properties: Ceftobiprole medocaril is produced through chemical modification of a fermentation product. Ceftobiprole medocaril is freely soluble in water. White to yellowish or slightly brownish powder. Ceftobiprole medocaril is a prodrug; the active moiety is ceftobiprole.

pH: The pH of a 1% solution in water is 4.52. pKa value of 2.8 at 25°C for carboxylic acid moiety of BAL5788. A second pKa at around 9 is assigned to the hydroximino (oxime) functional group.

CLINICAL TRIALS

Complicated Skin and Skin Structure Infections including Diabetic Foot Infections

Table 3 - Summary of Phase 3 clinical studies and patient demographics

Study No.	Trial design	Dosage, route of administration and duration	No. of subjects[a]	Demography: Gender Mean age (age range)
BAP00154 (Trial 1)	Randomized, double-blind study of ceftobiprole medocaril versus vancomycin in the treatment of cSSSI.	Treatment: i.v. infusion of ceftobiprole medocaril (500 mg ceftobiprole equivalent q12h over 60 min, or 1000 mg vancomycin q12h for 7 to 14 days	784	454 M, 330 W 47.3 yrs (18-91 yrs)
BAP00414 (Trial 2)	Randomized, double-blind study of ceftobiprole medocaril versus vancomycin plus ceftazidime in the treatment of cSSSI, including diabetic foot infections	Treatment: i.v. infusion of ceftobiprole medocaril (500 mg equivalents of ceftobiprole) q8h over 120 min plus placebo q12h over 60 min, or 1000 mg vancomycin q12h over 60 min plus 1000 mg ceftazidime q8h over 120 min for 7 to 14 days	828	523 M, 305 W 52.6 yrs (18-92 yrs)

[a] Intent-to-Treat analysis group

Surgical, traumatic and burn wound infections were present in 26% of patients, abscesses in 38%, cellulitis in 18% and non-limb threatening diabetic foot infections in 18% of patients at baseline. Only Trial 2 enrolled patients with diabetic foot infections (without evidence of osteomyelitis) comprising 31% of patients enrolled in this trial.

Study results

Table 4. Clinical Cure Rates at Test of Cure Visit[1] in a Phase 3 Trial in Complicated Skin and Skin Structure Infections

Trial 1: Gram-positive infections

Population	ZEFTERA 500 mg q12h			Comparator		
	N	Cured	%	N	Cured	%
Clinically evaluable	282	263	93.3	277	259	93.5
Intent-to-treat	397	309	77.8	387	300	77.5

[1] Test of cure visit 7 to 14 days after completing therapy

Table 5. Clinical Cure Rates at Test of Cure Visit[1] in a Phase 3 Trial in Complicated Skin and Skin Structure Infections

	Trial 2: Gram-positive and gram negative infections including diabetic foot infections					
Population	**ZEFTERA** 500 mg q8h			**Comparator**		
	N	Cured	%	N	Cured	%
Clinically evaluable	485	439	90.5	244	220	90.2
Intent-to-treat	547	448	81.9	281	227	80.8
Diabetic foot Infections	145	125	86.2	77	63	81.8

[1] Test of cure visit 7 to 14 days after completing therapy

Table 6. Clinical Cure Rate at TOC Visit[1] in Complicated Skin and Skin Structure Infections Caused by Gram Positive Pathogens Isolated at Baseline.

Pathogen	**ZEFTERA** 500 mg q12h % (n/N)[2]	**Comparator** % n/N[2]
Gram-positive		
Staphylococcus aureus (methicillin-susceptible)	96 (121/126)	96 (108/112)
Staphylococcus aureus (methicillin-resistant)	92 (56/61)	90 (54/60)
Streptococcus pyogenes	73 (8/11)	88 (15/17)

[1] Test of cure visit 7 to 14 days after completing therapy

[2] n is number cured; N is total

Table 7. Clinical Cure Rate at TOC Visit[1] in Complicated Skin and Skin Structure Infections Caused by Gram Positive and Gram Negative Pathogens, Including Diabetic Foot Infections, Isolated at Baseline.

Pathogen	**ZEFTERA** 500 mg q8h % n/N[2]	**Comparator** % n/N[2]
Gram-positive		
Staphylococcus aureus (methicillin-susceptible)	94 (150/160)	93 (84/90)
Staphylococcus aureus (methicillin-resistant)	90 (78/87)	86 (31/36)
Streptococcus pyogenes	90 (18/20)	92 (11/12)
Gram-negative		
Escherichia coli	89 (33/37)	92 (24/26)
Proteus mirabilis	75 (9/12)	90 (9/10)
Enterobacter cloacae	83 (10/12)	90 (9/10)
Klebsiella pneumoniae	82 (9/11)	100 (3/3)

[1] Test of cure visit 7 to 14 days after completing therapy

[2] n is number cured; N is total

There is limited experience in patients receiving more than 14 days of therapy (see **ADVERSE REACTIONS**).

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacodynamics

Safety Pharmacology
Safety pharmacology studies demonstrate that administration of BAL5788 (ceftobiprole medocaril) by i.v. infusion is associated with minimal or absent effects on cardiovascular, respiratory and CNS parameters at exposures exceeding those obtained in human clinical studies.

Central Nervous System
Convulsions were observed after administration of BAL 9141 directly into the brain in mice. The median effective dose (ED50) of BAL9141 (ceftobiprole) for centrally-mediated convulsions was determined to be 2.55 µg in a central nervous system (CNS) safety study in mice administered single intra-cerebroventricular (i.c.v.) injections of 0.3 to 30 µg BAL9141. The convulsant activity of ceftobiprole may be attributed to inhibition of GABA receptor-mediated neurotransmission. After intravenous (i.v.) bolus injection of BAL5788, doses ≤125 mg/kg were tolerated without effect. Signs of nephrotoxicity (related to drug precipitation in distal and collecting tubules) due to low solubility of the drug as early as 0.5 h after drug administration were reported. Reduced renal function manifested as high plasma levels of BUN in all along with increased creatinine in some animals and incidences of mortality were noted at doses ≥ 250 mg/kg. Delayed convulsions, also observed in mice at doses ≥250 mg/kg, were attributed to high levels of drug exposure (8 times greater than the human dose) caused by marked nephrotoxicity, which was considered to lead to reduced renal clearance of BAL9141, and thus, sustained elevated plasma and brain levels.

Respiratory System
BAL5788 had no effect on airway resistance (RL) or dynamic lung compliance (dyn) of respiratory function in anesthetized, ventilated Sprague-Dawley rats administered doses of 125, 250, and 500 mg/kg via a 4-h i.v. infusion.

Cardiovascular System
The cardiovascular (CV) safety of i.v. administered BAL5788 was evaluated in studies in hypertensive rats, conscious normotensive marmosets, and conscious beagle dogs. No drug-related CV effects were seen at 30 mg/kg (rats) or 35 mg/kg (marmosets). A slight, persistent increase in mean arterial blood pressure (MAP) was noted in rats and marmosets with a delayed onset following administration of a single i.v. bolus injection of BAL5788 at 100 mg/kg. At the 100-mg/kg dose level, a slight increase in heart rate (HR) was seen in marmosets, but not in rats. When marmosets were administered the same dose via a 1-h infusion, however, only a borderline effect was seen. No drug-related effects on CV parameters (heart rate, blood pressure, amplitude or interval of the ECG parameters) were noted in dogs (1 male and one female) receiving single i.v. doses of BAL5788 at 50 or 100 mg/kg via a 4-h infusion.

In a HERG assay, treatment with 5 µM BAL9141 produced no statistically significant inhibition of HERG tail current recorded from stably transfected HEK293 cells. The final concentration of BAL9141 tested in the HERG assay was 12.4 times below the Cmax observed in humans (approximately 62 µM, corresponding to 33 µg/mL). Due to low solubility of BAL9141,

concentrations higher than 5 μM could not be attained under conditions comparable with the HERG assay.

In vivo Protection Studies: Acute Infections Due to Gram-Positive and Gram-Negative Bacteria

Skin and Soft Tissue Infections

The efficacy of ceftobiprole against MSSA and MRSA was examined in a murine skin and soft tissue infection model. Female Skh-1 mice were injected s.c. on the left flank with 0.2 mL *S. aureus* Smith OC 4172 in brain heart infusion (BHI)-dextrin beads, and on the right flank with MRSA OC 8525 in BHI-dextrin beads. The animals received ceftobiprole subcutaneously. Ceftobiprole achieved a >1.7 log10 CFU/g reduction of MSSA in skin tissue compared to the initial inoculum at doses of 1.6 to 100 mg/kg/day. Against MRSA, ceftobiprole showed similar or improved reduction in bacterial load at doses of 1.6 to 100 mg/kg/day against comparators. Ceftobiprole was effective in reducing the lesion volume at the infection site in animals infected with either MSSA or MRSA.

Septicemia

The in vivo antibacterial efficacy of ceftobiprole was examined in a number of experimental murine septicemia infection models. Ceftobiprole was effective in treating experimental septicemia following subcutaneous administration, with ED50 values <3 mg/kg for strains with ceftobiprole MIC values ≤2 μg/mL. These strains include MSSA, MRSA (except MRSA 8525 for which the ED50 was 4.9 mg/kg), *E. coli*, *K. pneumoniae*, and *P. mirabilis*.

Rabbit Osteomyelitis Infection Model

The efficacy of ceftobiprole medocaril was examined in a rabbit model of MRSA osteomyelitis. A localized osteomyelitis was induced by a percutaneous injection of 10^6 CFU of MRSA 168-1. Two weeks post-infection, proximal tibial osteomyelitis was confirmed radiographically, and animals were randomized into 4 treatment groups (n=15/group). Animals in the ceftobiprole group were administered the equivalent of 40 mg/kg q8h of ceftobiprole. Four weeks of treatment were followed by a 2 week washout period. Tibias were recovered, bone matrix and marrow was cultured on blood agar plates and bacterial counts per gram of tissue was determined. In the ceftobiprole group, the MIC and MBC values for ceftobiprole were 0.39 and 6.25 μg/mL, respectively. Following ceftobiprole treatment bacterial titers in all infected left tibiae from evaluable rabbits were below the level of detection, whereas only 73% of infected left tibiae from comparator treated animals had bacterial titers below the level of detection; mean ceftobiprole titers were 3-5 times higher in infected left tibias than in uninfected right tibiae. These results indicate that ceftobiprole provided effective parenteral treatment of osteomyelitis cause by MRSA in this rabbit model.

Pharmacokinetics

The oral absorption of BAL 5788 and its active BAL9141 has been investigated in rats. Oral bioavailability of BAL9141 and its pro-drug BAL5788 was very low (<1%) after a single p.o. dose of BAL5788 or BAL9141 in aqueous solutions. BAL9141-related radioactivity was rapidly distributed to tissues of rats and mice following administration of a single i.v. bolus dose of radiolabelled BAL9141. The highest levels were found in kidney (tissue to plasma ration = 1.3) followed by tooth pulp, liver, skin and lung. Penetration to the brain was minimal (tissue to plasma ratio = 0.01). Analysis of homogenates from brain and kidney showed that BAL9141

was the main component detected, indicating that the active drug rather than any predominant metabolites was responsible for the CNS and renal effects observed after administration of BAL5788. The elimination of radioactivity from tissues occurred in parallel to elimination from the blood, predominantly by renal excretion in the urine. There was no retention in any tissues with the exception of the kidney cortex in rats where the level at 48h post dose was 20% of that seen at the peak level, which occurred at 0.25h. There was no retention in pigmented tissues including the eye and skin of pigment rats.

Metabolism of BAL5788 under in vitro conditions by different species resulted in hydrolytic cleavage of the carbamate moiety of BAL5788. The main metabolic reaction of BAL9141 was hydrolysis of the β-lactam ring of the drug RO65-2070. Metabolism of BAL 9141 during 24 hours was 59% in mouse, 64% in marmosets, 51% in humans, and 48% in rat and 43% in dog. Metabolic profiles were similar to those in hepatocytes. Excretion of BAL9141 was similar to glomerular filtration rate in all animal species. Elimination $t_{1/2}$ ranged from 0.29 hr in mouse to 1.7 hour in cynomolgus monkeys. In rats, excretion of radioactivity in feces was 17%, in cage wash, GI Tract, and residual carcass was < 3% at 96 hrs post-dose.

Pharmacokinetic/Pharmacodynamic Parameters
Similar to other ß-lactam antimicrobial agents, the time that the plasma concentration of ceftobiprole exceeds the MIC (%T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic studies. For gram-positive bacteria (including 4 staphylococci and 4 pneumococci), the mean %T>MIC for ceftobiprole was 20 to 22% for a static dose. For gram-negative bacteria, the mean %T>MIC for stasis was 43% for 4 strains of Enterobacteriaceae and 58.6% for a representative isolate of ***P. aeruginosa***.

HUMAN PHARMACOLOGY

***In vitro* studies**

Plasma Protein Binding
Two studies were conducted using human plasma spiked with ceftobiprole. The protein binding of ceftobiprole was considered to be low, ~16%, and is independent of ceftobiprole concentration across the range of 0.5 to 100 µg/mL. Ceftobiprole at a concentration of 25 µg/mL (12.5 µM) is primarily bound to albumin (6.5% to 11.5%, i.e. 0.8 to 1.4 µM bound), and also bound to α-1 acid glycoprotein (4.8% to 6.8%, i.e. 0.6 to 0.9 µM bound). Binding of ceftobiprole to both proteins is low compared to their normal molar concentrations (albumin 530-760 µM; α-1 acid glycoprotein 10-40 µM).

In vitro Metabolism
In a degradation study, conversion of ceftobiprole medocaril to ceftobiprole was very rapid ($t_{1/2}$ within 10 to 54 seconds) in the plasma of marmosets, cynomolgus monkeys, mice, and humans. In human plasma, the $t_{1/2}$ was observed to be 38 seconds. Inhibition studies with ethylenediaminetetraacetic acid (EDTA) suggested that type A plasma esterases are involved in the cleavage of ceftobiprole medocaril to ceftobiprole. Cleavage of ceftobiprole medocaril to ceftobiprole was not inhibited by acetycholinesterase inhibitors such as neostigmine at 0.1 µg/mL, and moderately inhibited by dichlorvos, a known Type B esterase inhibitor. Rapid cleavage of ceftobiprole medocaril to ceftobiprole was also observed when ceftobiprole

medocaril was incubated with hepatocytes derived from rats, dogs, cynomolgus monkeys, marmosets, and humans. Since hepatic conversion is not the sole pathway, type A esterases should be able to convert ceftobiprole medocaril to the active ceftobiprole in patients with hepatic impairment.

Pharmacodynamics

Study Measuring the Effects of QT and Corrected QT(QTc) Intervals

QT/QTc Study

In a QT/QTc study conducted in healthy subjects, the effect of ceftobiprole on QT/QTc interval prolongation was similar to that of placebo after administration of single intravenous therapeutic (500 mg) and supratherapeutic (1000 mg) doses. Ceftobiprole had no effect on heart rate or other ECG parameters in healthy adults.

Pharmacokinetics

Following administration of ceftobiprole at doses of 500 mg to 1000 mg given over 30 minutes, peak concentration (C_{max}) and area under the curve (AUC) increased proportionally with dose. Estimates of total systemic clearance (CLs), volume of distribution at steady state (V_{SS}), and $t_{1/2}$ were consistent across the dose range of 125 mg to 1000 mg, suggesting that the pharmacokinetics of ceftobiprole were linear and predictable. Approximately 60% to 80% of the dose was recovered in urine as unchanged ceftobiprole.

Table 8: **Mean (SD) Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Infusions of Ceftobiprole**

Dose (mg)	Infusion Duration	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg•h/mL)	$t_{1/2}$ (h)	V_{SS} (L)	CL_S (L/h)
500	0.5h	40.6 (7.38)	101 (9.04)	3.63 (0.48)	16.4 (2.11)	4.99 (0.46)
500	1h	34.2 (6.05)	116 (20.2)	2.85 (0.55)	11.0 (2.93)	4.46 (0.84)
500	2h	29.2 (5.52)	104 (13.9)	3.1 (0.3)	21.7 (3.37)	4.89 (0.687)
750	0.5h	60.7 (4.55)	156 (19.3)	3.64 (0.32)	16.3 (1.82)	4.85 (0.57)
1000	0.5h	72.2 (8.78)	151 (9.04)	3.25 (020)	18.9 (2.31)	6.64 (0.41)
1000	2h	46.2 (8.20)	187 (30.1)	3.2 (0.5)	25.4 (5.48)	5.48 (0.897)

After repeated administration (q8h or q12h for up to 12 days), the pharmacokinetic properties of ceftobiprole were time independent. The observed accumulation factor ranged from 1.02 to 1.16 across studies, suggesting minimal accumulation from single to multiple doses. Overall the pharmacokinetics of ceftobiprole appeared to be independent of the infusion duration and the dosing interval.

Table 9: **Mean (SD) Ceftobiprole Pharmacokinetic Parameters Following Multiple Intravenous Infusions of Ceftobiprole**

Dose (mg)	Infusion Duration	τ	C_{max} (μg/mL)	AUC_{τ} (μg•h/mL)	$t_{1/2}$ (h)	V_{SS} (L)	CL_{SS} (L/h)
500	0.5h	q12h	44.2 (10.8)	102 (20.0)	4.04 (0.31)	16.7 (3.58)	5.06 (0.95)
500	2h	q8h	33.0 (4.83)	102 (11.9)	3.3 (0.3)	15.5 (2.33)	4.98 (0.58)
750	0.5h	q12h	60.6 (9.99)	156 (11.1)	4.11 (0.41)	16.1 (2.20)	4.83 (0.34)
1000	2h	q8h	37.9 (7.25)	141 (35.2)	3.4 (0.4)	24.9 (5.0)	7.50 (1.74)

Factors Influencing the Pharmacokinetics

Special Populations

Renal Insufficiency

Following a single infusion of ceftobiprole 250 mg over 30 minutes, systemic exposure in terms of AUC was 29% higher in subjects with mild renal impairment, and 2.5-fold, and 3.3-fold higher in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function. Total systemic clearance (CL_s) and renal clearance (CL_R) decreased with decreasing renal function such that the greatest reductions were noted in the moderately (62% for CL_s and 78% for CL_R) and severely (75% for CL_s and 91% for CL_R) renally impaired groups. Urinary recovery ranged from 74% to 32% in subjects with mild to severe renal impairment. Elimination half-life increased with decreasing renal function, such that subjects with severe renal impairment exhibited the longest $t_{1/2}$ of 11 hours.

Table 10: Mean (SD) Ceftobiprole Pharmacokinetic Parameters In Healthy Subjects And Subjects With Various Degrees of Renal Impairment After a Single Intravenous Infusion of Ceftobiprole 250 mg For 30 Minutes (Study BAP00018; N=20)

	Renal Function			
	Normal	Mild	Moderate	Severe
Parameter	CL_{CR}: >80 mL/min N=5	CL_{CR}: 50-80 mL/min N=5	CL_{CR}: 30-<50 mL/min N=5	CL_{CR}: <30 mL/min N=5
C_{max} (μg/ml)	20.6 (2.06)	20.1 (1.45)	24.4 (1.65)	22.8 (3.48)
$AUC_{0-\infty}$ (μg•h/ml)	52.8 (6.91)	74.8 (15.6)	151 (21.6)	222 (71.00)
$t_{1/2}$ (h)	3.45 (0.37)	4.75 (0.81)	6.87 (1.12)	11.1 (1.96)
V_{SS} (L)	15.8 (1.81)	18.0 (0.76)	14.2 (0.80)	16.9 (2.39)
CL_S (L/h)	4.80 (0.61)	3.46 (0.71)	1.68 (0.25)	1.21 (0.36)

Gender

Systemic exposure to ceftobiprole was higher in females (Single dose: 32% for Cmax and 21% for AUC; Multiple dose: 16% for Cmax and 11% for AUC) than in males. Estimates of CLs and Vss were 15% and 20% lower, respectively in females as compared with males. Renal clearance and urinary excretion of ceftobiprole (83%) were similar in both genders. When these parameters were adjusted for body weight, parameter estimates between males and females were comparable.

Systemic exposure to the open-ring metabolite was lower than that of ceftobiprole, accounting for approximately 4% parent ceftobiprole exposure, and increased approximately 33% for Cmax and 48% for $AUC_{0\text{-}8h}$ from Day 1 to Day 5, with an accumulation ratio of 1.5. The elimination half-life of the open-ring metabolite was slightly longer, ~5 hours, than ceftobiprole which was ~3 hours. Systemic exposure to ceftobiprole and the open-ring metabolite was higher in females compared to males, which normalized upon correction for dose per kg body weight.

Table 11: **Mean (SD) Ceftobiprole Pharmacokinetic Parameters Following Single and Multiple (q8h) 2 Hour Intravenous Infusions of Ceftobiprole 500 mg in Healthy Males and Females**

	Single Dose		Multiple Dose	
Parameter	Male	Female	Male	Female
t_{max} (h)	1.97	1.97	1.91	1.97
C_{max} (μg/mL)	25.2 (2.92)	33.3 (4.36)	30.6 (4.59)	35.5 (3.71)
AUC (μg•h/mL)	95.8 (10.5)	112 (12.0)	96.2 (9.66)	107 (11.7)
$t_{1/2}$ (h)	3.2 (0.3)	3.0 (0.1)	3.5 (0.3)	3.2 (0.3)
V_{ss} (L)	24.0 (2.76)	19.4 (2.14)	17.2 (1.75)	13.7 (1.19)
CL_s (L/h)	5.28 (0.62)	4.50 (0.52)	5.25 (0.55)	4.70 (0.49)

Pharmacokinetic/Pharmacodynamic Parameters
After single 30-minute i.v. infusion of 500 mg, 750 mg and 1000 mg doses, the mean %T>MIC for unbound ceftobiprole concentration ranged from 58%, 60% and 85%, respectively.

For the regimen of 500 mg administered 3 times daily as a 2-hour infusion, the probability of target attainment assuming a fixed MIC of 4 μg/mL exceeded 89% for both the 30% and 50% T>MIC targets in subjects with normal renal function. For the regimen of 500 mg administered twice daily as a 1-hour infusion, the probability of target attainment assuming a fixed MIC of 4 μg/mL exceeded 89% for the 30% T>MIC target, in subjects with normal renal function , which is needed for activity against gram positive infections.

MICROBIOLOGY

Ceftobiprole medocaril is the prodrug of ceftobiprole, which is rapidly converted in vivo to the active antibacterial agent ceftobiprole. It was not possible to determine the in vitro antibacterial activity of the prodrug.

Mode of Action
Ceftobiprole is an expanded spectrum cephalosporin with activity against gram-positive and gram-negative aerobic bacteria, including methicillin-resistant *S. aureus* (MRSA). Ceftobiprole, a semi-synthetic cephalosporin antibiotic, has a bactericidal mode of action that involves tight binding to essential penicillin-binding proteins (PBPs) in gram-positive and gram-negative bacteria, thereby preventing completion of cell wall biosynthesis. In gram-positive bacteria, ceftobiprole differs from other cephalosporins and β-lactams due to its unique high affinity for PBP2a from methicillin-resistant staphylococci. Ceftobiprole has high affinity for the essential PBP 3 and PBP2 of *E. coli*.

Development of Resistance

Ceftobiprole evades both of the two major mechanisms of β-lactam resistance in staphylococci, (i.e. the production of an acquired PBP with reduced affinity for β-lactams and β-lactamase mediated drug hydrolysis) as it binds strongly to PBP2a and is not readily hydrolyzed by the staphylococcal penicillinases. Ceftobiprole is stable to hydrolysis by many Class A B-lactamases, such as staphylococcal penicillinases, TEM-1, TEM-2 and SHV-1, and Class C B-lactamases, i.e., AmpC cephalosporinases produced by gram-negative bacteria. However, ceftobiprole is not stable to most extended-spectrum β-lactamases (ESBLs) from the TEM, SHV and CTX-M families, to serine carbapenemases such as KPC or SME enzymes or to metallo-β-lactamases including members of the IMP or VIM families. Ceftobiprole also appears to be hydrolyzed by beta-lactamases from anaerobic bacteria.

Ceftobiprole demonstrated low propensity for resistance in both single step and serial passage resistance experiments.

In vivo use of ceftobiprole treatment in animal models of infection conducted in rat, mouse, and rabbit, did not produce resistant mutants of *S. aureus*, *E. cloacae* and ESBL-negative *K. pneumoniae* during the treatment periods.

Spectrum of Activity

Ceftobiprole has demonstrated *in vivo* and *in vitro* activity against a broad spectrum of gram-positive and gram-negative bacteria. Table 12 indicates the *in vitro* activity of ceftobiprole against strains of microorganisms for which clinical efficacy have been determined.

Table 12: *In vitro* activities of ceftobiprole against organisms for which the clinical efficacy of ceftobiprole has been demonstrated.

Organism	# of isolates	MIC (µg/mL)		
		Range	50%	90%
Staphylococcus aureus (MSSA)	737	≤0.06-1	0.25	0.5
Staphylococcus aureus (MRSA)	730	≤0.06-4	1.0	2
Streptococcus pyogenes	10	≤0.008-0.12	0.03	0.06
Enterobacter cloacae	88	0.03->32	≤0.12	≤0.12
Escherichia coli	517	≤0.06->8	≤0.06	≤0.06
Klebsiella pneumoniae	79	≤0.016-16	≤0.06	≤0.25
Proteus mirabilis	60	≤0.06-0.25	≤0.06	≤0.06

Table 13 indicates the *in vitro* activity of ceftobiprole against clinical isolates, however the efficacy of ceftobiprole in treating clinical infections due to these microorganisms has not been established in clinical trials.

Table 13: *In vitro* activities of ceftobiprole against clinical isolates for which clinical efficacy has not been demonstrated.

Organism	# of isolates	Range	MIC (µg/mL) 50%	90%
Gram-positive				
Enterococcus faecalis (VSE)	413	≤0.06->8	0.5	1
Staphylococcus epidermidis	33	0.12 - 1	0.25	1
Streptococcus agalactiae	15	0.016-0.03	0.016	0.016
Coagulase-negative staphylococci (inc. *S. haemolyticus, S. hominis, S. lugdunensis, S. saprophyticus*)	116	≤0.016 - 1	0.12	1
Streptococcus pneumoniae				
penicillin-susceptible	291	≤0.016-0.03	≤0.016	≤0.016
penicillin-resistant	209	0.016-4	0.5	1
Viridans group streptococci	54	≤0.016-0.06	≤0.016	0.06
Gram-negative				
Enterobacter spp.	163	≤0.06->8	≤0.06	4
Haemophilus influenzae	435	≤0.12-0.5	≤0.12	≤0.12
Moraxella catarrhalis	206	≤0.008-1	≤ 0.12	1
Neisseria gonorrhoeae	51	≤0.008 - 0.12	0.03	0.06, 0.12
*Pseudomonas aeruginosa**	68	0.12-16	2	8

* Unpublished surveillance studies of North American sites (including Canadian sites) reported isolates with a ceftobiprole MIC > 8µg/mL.

Susceptibility Test Methods

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. Standardized procedures are based on dilution method (broth, agar or microdilution) or equivalent using standardized inoculum and concentrations of ceftobiprole. [1] The MICs should be interpreted according to the criteria provided in Table 14.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. This procedure uses paper disks impregnated with 30 mg ceftobiprole to test the susceptibility of microorganisms to ceftobiprole. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ceftobiprole. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 µg ceftobiprole disk should be interpreted according to criteria provided in Table 14.

Table 14: Susceptibility Interpretive Criteria for Ceftobiprole

	Minimum Inhibitory Concentrations (μg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤4	--[a]	--	>16	--	--
Streptococcus spp. other than *S. pneumoniae*	≤0.5	--	--	>19	--	--
Enterobacteriaceae	≤1	2	4	>20	18-20	<18

S=Susceptible, I=Intermediate, R=Resistant

[a]The current absence of data on resistant strains precludes defining any category other than 'Susceptible'. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

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

Note: Methicillin-resistant *Staphylococcus* spp. should be considered susceptible to ceftobiprole if the MIC is in the susceptible range irrespective of the oxacillin test or mecA detection results. Specialized testing conditions in media supplemented with 2% NaCl at 30ºC to induce mecA production may result in one fold increase in MIC.

Quality Control

Standardized susceptibility test procedures require the use of control microorganisms to control the technical aspects of the test procedures. For the diffusion technique, the 30 μg ceftobiprole disk should provide the following zone diameters provided in Table 15 below.

Table 15 : Quality Control Microorganisms and corresponding MIC/Disk diffusion ranges

	MIC (μg/mL)	Disk Diffusion (Zone Diameter in mm)
S. aureus ATCC 29213	0.25-1	Not applicable
S. aureus ATCC 25923	Not applicable	26-34
E. coli ATCC 25922	0.03-0.12	30-36
S. pneumoniae ATCC 49619	0.004-0.03	33-39

TOXICOLOGY

The toxicology of BAL5788 (ceftobiprole medocaril) was characterized in repeated-dose toxicity, mutagenicity, fertility, developmental toxicity, and pre- and postnatal toxicity studies, and in studies assessing local tolerability, potential antigenic and hematolytic effects, phototoxicity, and nephrotoxicity. Effects noted in animal toxicity studies occurred at high doses and included reversible renal toxicity due to drug precipitates at urine concentrations 5-10 fold higher than in humans, and convulsions.

No single dose toxicity studies were conducted. Pilot 3-Day toxicity studies were conducted utilizing bolus, continuous and intermittent IV administration for evaluation of initial dose selection for repeat dose toxicity studies. Over dosage in these studies was associated with renal toxicity, decreased renal function and seizures.

In a 4-week infusion study (4 h) in rats, once daily (q.d.) doses of BAL5788 were well tolerated up to 360 mg/kg/day. Dose-dependent minimal to slight cytoplasmic inclusions seen in renal proximal tubules at doses ≥250mg/kg/day were not associated with any functional or other morphological changes in the kidneys, and were fully reversible following a 4-week recovery period. Based on these findings, the No Observed Adverse Effect Level (NOAEL) in this study was 360 mg/kg/day, a 12x multiple of the clinical dose. In a similar study in marmosets, doses of up to 200 mg/kg were well tolerated, with a NOAEL of 100mg/kg/day, a 3x multiple of the clinical dose. Minor and reversible changes (i.e., slightly increased blood urea nitrogen [BUN] levels, minimal occurrence of brown pigment in the distal tubular epithelium of the kidneys) were noted at 200 mg/kg/day. In a 2-week study in dogs, dose-dependent histaminergic reactions were observed, and these were attenuated by prolongation of the infusion duration from 0.5h to 2h following the first day of dosing. Slight eosinophilic droplets were observed in the proximal tubule epithelium in the kidney at 50 and 100 mg/kg/day. The NOAEL was below 25 mg/kg due to the occurrence of slight histaminergic reactions.

In a 13-week study in rats, toxicity to the kidneys was observed at doses ≥250 mg/kg with incidences of mortality due to acute renal failure observed at 250, 500 and 750 mg/kg/day, and was associated with the precipitation of drug-like material in the distal part of the nephron. Findings in the kidneys were dose-related and trended towards recoverability after 4 weeks. The NOAEL in this study was 125 mg/kg/day (a 4x multiple of the clinical dose). A 3-month repeat dose study in marmosets vomiting and reversible renal proximal tubule pigmentation were observed at 100 and 200 mg/kg and increases in plasma AST and LDH were observed at 200 mg/kg. The NOAEL was 100 and 50 mg/kg/day for males and females, respectively (3.3x and 1.7x multiples of the clinical dose, respectively. In a 13-week infusion toxicity study in beagle dogs at doses of 8 and 32 mg/kg/day, clogging of the surgically implanted cannula, resulting in an inability to dose, was the proximal cause of the premature sacrifice of 5 out of 6 dogs administered the q.d. (2-h) dose of 32 mg/kg BAL5788. No findings of toxicological importance were observed in these 5 animals, which received doses for 4 to 11 weeks. Clinical observations during the study were similar to those seen in the 2-week study in dogs, and consisted of findings of discolored urine seen at doses of 8 and 32 mg/kg (equivalent to one quarter of the clinical 500 mg TID dose, and one-fifth the clinical 500 mg BID dose), and of reddening of the skin and mucous membranes, which was attributed to histamine release. The NOAEL was 8/mg/kg/d (approximately 75% less than the clinical dose).

Carcinogenicity
Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of ceftobiprole.

Mutagenicity / Genotoxicity
The genotoxic potential of BAL5788 and/or BAL9141 (ceftobiprole) was examined in a battery of in vitro (Ames, mouse lymphoma/thymidine kinase [ML/TK], human chromosome aberration [HCA]) and in vivo (mouse micronucleus test [MNT] and rat unscheduled DNA synthesis [UDS]) assays. BAL5788 exhibited clastogenic activity in the ML/TK test at cytotoxic concentrations after 3h incubation at 750 and 500 ug/ml (with and without metabolic activation respectively) and at 150 ug/ml at 24 h exposure period (without metabolic activation). BAL9141 induced an equivocal effect at high concentrations (2000µg/mL). In the HCA assay, BAL5788, but not BAL9141, was clastogenic under the described in vitro conditions at cytotoxic concentrations. The positive response was most probably attributed to the cleavage product diacetyl with no contribution from the active cephalosporin BAL9141. No genotoxic activity was seen in the *in vivo* micronucleus assay in mouse bone marrow and in an unscheduled DNA synthesis (UDS) by the uptake of radio-labelled thymidine assayed autoradiographically by utilizing 200 or 500 mg/kg Ro 65-5788. The in vitro genotoxic activity of diacetyl and other dicarbonyl compounds is thought to be mediated by an oxidative mechanism of action due to the formation of oxygen radicals. The presence of multiple anti-oxidative defense mechanisms in vivo, that are not present in the in vitro test systems, helps to account for the absence of genotoxicity in vivo. Furthermore, diacetyl, which is produced endogenously in humans, is rapidly metabolized in vivo by oxidoreductases acting on carbonyl compounds, resulting in the formation of nontoxic glycol metabolites. Based on these observations, a genotoxic liability of BAL5788 in man is not likely.

Teratogenicity / Impairment of fertility
BAL5788 was neither teratogenic nor embryotoxic in rats and cynomolgus monkeys after i.v. infusion of doses up to 360 mg/kg/day (4 h) and 120 mg/kg/day (2 h), respectively, and had no effects on fertility and early embryonic development in rats after i.v. infusion of doses up to 360 mg/kg/day (4 h). In cynomolgus monkeys, reduced litter size and survival rate was observed at doses that cause maternal toxicity. Studies in rats have shown that the concentration of ceftobiprole excreted in animal milk is 20% of the maternal plasma levels. In a pre- and postnatal toxicity study in rats administered BAL7588 via i.v. infusion (4 h), the NOAEL in dams (F0 generation) was 175 mg/kg (a 6x multiple of the clinical dose) for maternal toxicity and 250 mg/kg/day (a 8x multiple of the clinical dose) for reproductive toxicity. Functional and physical development of the F1 and F2 generations was normal in all groups.

Other Studies:
Antigenicity
In a guinea pig antigenicity study, signs of potential antigenicity were seen at i.v. bolus doses ≥20 mg/kg or at subcutaneous (s.c.) doses of 50 mg/kg in combination with adjuvant.

In a 2-week study in dogs, reddening of the skin and mucous membranes was observed which was attributed to histamine release. The NOAEL was 8 mg/kg/day, which is 75% less than the clinical dose.

Hematolytic Effects

No hemolysis or precipitation was observed in *in vitro* testing of dog plasma at concentrations ≤1.25%. At higher concentrations, however, observations of hemolysis and marked to moderate plasma turbidity and precipitation were observed, and were similar to increased adverse reactions of precipitation, flocculation and coagulation seen in *in vitro* dilution of human, rat or marmoset plasma at concentrations ≥12.5 mg/mL. The results demonstrate that concentrations ≥12.5 mg/mL (a 6x multiple of the clinical concentration) cause blood hemolysis and plasma precipitation and flocculation, which may be increased with increasing infusion volume, repeated dosing and or increasing infusion duration.

Infusion Site Reactions

Three 13-week infusion toxicity studies were conducted in rats, beagle dogs, and marmosets. In rats administered BAL5788 via a q.d. 4-h infusion, the primary targets of toxicity were the kidneys and the infusion site, where local irritation and the presence of a yellowish-brown fibrinous material at the tip of the catheter were associated with thrombus formation. Similar dose-related venous irritation was also observed in the marmoset study (BAL5788 dosed q.d. 4-h infusions). In these studies, physical irritation of the veins by the catheter, possibly in combination with additional effects due to obstruction of blood flow, was considered to predispose the vessel wall to irritation from the compound; these effects were considered to be exacerbated by the length of the treatment period and by the infusion of high concentrations of test article, and they resulted in the release of emboli from thrombi at the injection site. Incidences of mortality attributed to thrombo-embolic changes in male rats were observed at 250, 500 and 750 mg/kg/day. In marmosets, mortalities were observed at 50, 100, and 200 mg/kg/day, and were preceded by a general decline in physical condition and convulsions.

Nephrotoxicity

Cephalosporin-specific nephrotoxicity was not observed in rabbits.

Phototoxicity

The potential for a phototoxic skin response in humans is considered to be low, as results from both an in vitro test in cultured mouse fibroblasts and from an in vivo test in hairless rats revealed that neither BAL9141 nor BAL5788 exhibited phototoxic potential following ultraviolet A (UVA) irradiation.

A summary of toxicology studies is presented in table 16.

Table 16: Summary of toxicology studies

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
3-Day Pilot Study (116P97)	Rat; Wistar; 3 males/group	IV – slow bolus; BAL 5788	Ranging from 0 to ,200 mg/kg, t.i.d.	Effects seen at lower (<100 mg/kg) primarily consisted of Cytoplasmic inclusions (mild) in proximal renal tubules. Effects seen at > 100 mg/kg included: mild ↓ body weight, moderate ↑ BUN, ↓ triglycerides, kidneys pale and enlarged with yellow foci, on microscopic examination moderate findings included dilation, vacuolation and basophilia of the distal tubules as well as distal tubule single cell necrosis, increased mitotic rate and intraluminal deposits; and cytoplasmic inclusions (mild) in proximal renal tubules.
3-Day Pilot Study 131P97	Rat; Wistar 2 males (control) 4 males, 2 females 2 males, 1 female	IV continuous infusion;	0, 600 mg/kg	600 mg/kg/day: Kidneys pale and enlarged, dilation, vacuolation and basophilia of the distal tubules, cytoplasmic inclusions (mild) in proximal renal tubules. Terminal BAL9141 plasma concentration at 0.08 hours (after termination of infusion) 42.5/37.4 µg/mL; at 1 hour (after termination of infusion) 11.5/13.2 µg/mL.
3-Day Pilot Study 207P98	Rat; Wistar; Control and High Dose: 5 males/group Low Dose: 7 males 2/group held for 14 day recovery period 1 male	Intermittent IV infusion; BAL5788	0, 250 b.i.d., 500 b.i.d.	250 mg/kg (b.i.d.) [12.5X clinical dose]: kidneys pale and enlarged with granulated surface, urinary bladder contents yellow-orange, on microscopic examination cytoplasmic inclusions were noted (mild) in proximal renal tubules. Plasma concentration of BAL9141 was 60.2 ug/mL. Brain concentration at termination was 0.33µg/mL. 500 mg/kg (b.i.d.) intermittent intravenous infusion: Following a 2-week recovery period distal tubule intraluminal deposits and increased tubular basophilia were evident. Individual BAL9141 plasma concentration 3 hours into the second 4-hour infusion on day 3: 209 µg/mL.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
3-Day Pilot Study 817P97	Primate; marmoset; Placebo: 2 Males Low Dose: 1 Male Mid Dose: 3 Males High Dose: 1 Male	Intravenous injection - slow bolus; 0.9% sodium chloride/citric acid, NaOH/ BAL5788 plus vehicle	0, 20, 100, 200 mg/kg t.i.d.	Animal administered 20 mg/kg (t.i.d.) showed intermittent limb tremors on day 3. In animals administered 100 or 200 mg/kg (t.i.d.): One animal killed in extremis following 7 doses (100 mg/kg), and one animal killed in extremis (200 mg/kg). Microscopically kidney findings were characterized by basophilia, hyperplasia, hypertrophy, single cell necrosis and increased mitoses of epithelial cells of cortical and medullary distal and collecting tubules. Dilation of cortical distal tubules, and brownish intraluminal deposits within cortical and medullary distal and collecting tubules were also noted. 200 mg/kg (t.i.d.): There were no adverse effects at the injection sites that were attributed to injection of BAL5788. The limited plasma level monitoring of BAL9141 indicated that the marmosets were exposed to about the extent predicted from preliminary rat pharmacokinetics. Slightly higher plasma concentrations were found at higher dose levels. Occasional clonic convulsions were noticed with 200 mg/kg doses.
3-Day Pilot Study 903P99	Primate; marmosets; 3 males/group	Intermittent intravenous infusion; 0.9% sodium chloride/citrate buffer/BAL5788 plus vehicle	Three days (two 4 hour infusion periods/day at 12 hour intervals); 0, 250 mg/kg b.i.d. (2mL/kg/hour)	250 mg/kg (b.i.d.): Test article colored urine evident in all treated animals. Mean BAL9141 plasma concentration 3 - 4 hours into the first and last 4-hour infusion: 181.1/173.3 µg/mL (first/last infusion).
Repeat Dose Study 1003097	Rat; 40 males	i.v. infusion (4 h) BAL5788	2 weeks + 4 weeks recovery 0, 175, 250, 360 (b.i.d.) mg/kg	The non-toxic dose level of BAL5788 was 175 mg/kg/4h at which no necrotic or degenerative changes were observed in the kidneys.
Repeat Dose BAP00046	Rat; 5 male and 5 female per dose group 3 male and 3 female for recovery group	i.v. infusion (4h) BAL5788	0, 175, 250, 360 mg/kg	No significant toxic changes were noted following administration of BAL5788 at 250 mg/kg/4h. All changes noted during the dosing period disappeared during the 4-week recovery period.
Repeat Dose BAP00728	Rat; 10-15 male and 10-15 female per dose group	i.v. infusion (4-8hr) BAL5788	13 weeks + 4 weeks recovery 0, 125, 250, 376, 500, 750 mg/kg	At >250 mg/kg/d dose, 5 animals died due to acute renal failure and thrombolytic effects. Occasional clonic convulsions and kidney changes were noticed with ≥125 mg/kg/d dose. The non-toxic dose level of BAL5788 was considered to be 125 mg/kg/day for both males and females (~4.2 times the clinical dose).

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Repeat Dose BAP00230	Dog/Beagle 3 male, 3 female per dose group (2 male, 2 female for 100 mg/kg group)	i.v. infusion 30 minutes changed to 2 hours BAL 5788	2 weeks + 2 weeks recovery 0, 25, 50, 100 mg/kg	Dose dependent vomiting and reddening of the skin which was observed which was attenuated by extension of dosing duration. No precipitation was noted in the kidneys despite high urine concentrations of BAL 9141.
Repeat Dose TOX7918	Dog/Beagle 6 male, 6 female low dose group; 3 male, 3 female high dose group	i.v. infusion (2 h) BAL5788	13 weeks 0, 8, 32 mg/kg	Doses of 8 or 32 mg/kg/day caused minor treatment related reddening of the skin during the first 4 weeks of treatment that were associated with histamine release at the 32 mg/kg/day level. A dose level of 8 mg/kg/day was considered to be the NOAEL based on these findings. This dose is ~25% of the clinical dose.
Repeat Dose 1003329	Marmoset 3 male /group	i.v. infusion (4 h) BAL5788	2 weeks 0, 175, 250, 360 mg/kg/h (b.i.d)	The non-toxic dose level of BAL5788 was considered to be less than 175 mg/kg/h since organic changes (precipitates in the distal and collecting tubules, increased mitosis in the collecting tubule, and brown pigment in the collecting tubules) were noted in the kidney at this dose level.
Repeat Dose 1003800	Marmoset/*Callithrix jacchus* 3 males/group; 6 males for recovery period	i.v. infusion (4 h, 2 x per day, q12) BAL 5788	2 weeks + 4 weeks recovery 0, 50, 100, 250 mg/kg (b.i.d)	No significant toxic changes were noted following the administration of BAL5788 at 100 or 50 mg/kg/4h. Mortality (n=1), vomiting, discoloured urine, deposition of brown pigment in tubular epithelium was observed with 250 mg/kg/d dose.
Repeat Dose BAP00045	Marmoset/*Callithrix jacchus* 3 male, 3 female/dose group; 6male, 6 female for recovery period	i.v., infusion (4 h) BAL5788	4 weeks + 4 weeks recovery 0, 50, 100, 200 mg/kg	No significant changes were noted following the administration of BAL5788 at 100 mg/kg/4h. NOAEL was 100 mg/kg/d. All changes noted during the dosing period disappeared during the 4-week recovery period. In the 200mg/kg group, abnormal urine colour and brown pigment in the tubular epithelium of the kidneys was observed.
Repeat Dose TOX7154	Marmoset/*Callithrix jacchus* 8 male, 8 female for high dose; 5 male, 5 female low and mid-dose	i.v., infusion (4 h) AL 5788	13 weeks + 4 weeks recovery 0, 50, 100, 200 mg/kg/d	The indwelling catheter caused vascular irritation at the infusion site in all groups which was exacerbated by the infused test article resulting in the formation of local thrombi. The non-toxic dose levels of BAL5788 were considered to be 100 mg/kg/day (~3.3 times clinical dose) and 50 mg/kg/day (~1.7 times clinical dose) for males and females. In the 50 mg/kg/d group, 3 animals died.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Genotoxicity Reverse point mutation (Ames Test) (B-167'797)	*Salmonella typhimurium*; TA98, TA100, TA1535, TA97, TA102	In vitro BAL5788	BAL5788: 1, 3.16, 10, 31.6, 100 µg/plate	Cytotoxic Effects: strain dependent toxic effects starting at 31.6 µg/plate, with the exception of TA1535, where toxic effects started at 1 µg/plate. Genotoxic Effects: No
Genotoxicity Forward gene mutation of TK locus (B-167'775)	Mouse lymphoma cells	In vitro BAL9141	BAL9141: 39.06 to 5000 µg/mL	Cytotoxic Effects: Toxicity was observed at doses =2000 µg/mL (3 h: -S-9) and = 1250 µg/mL (3 h:+S-9). Genotoxic Effects: Weakly positive (equivocal) effect at toxic concentrations = 3000 µg/mL (3 h: -S-9) and =2500 µg/mL (3 h: +S-9). BAL9141 induced an equivocal, positive effect with and without metabolic activation
Genotoxicity Forward gene mutation of TK locus (B-169'336)	Mouse lymphoma cells	In vitro BAL5788	BAL5788: 125 to 1250 µg/mL	Cytotoxic Effects: Toxicity seen after 3 h (-S-9/+S-9: 500 and 750 µg/mL) and 24 h (-S-9: 150 µg/mL) treatment with BAL5788. Genotoxic Effects: The mutation frequency increased at cytotoxic BAL5788 doses due to enhanced numbers of small colonies, indicating clastogenic activity.
Genotoxicity Chromosome aberration (B169'918)	Human peripheral blood lymphocytes	In vitro BAL5788, BAL9141, diacetyl	BAL5788: 250 to 1000 µg/mL BAL9141: 312. 5 to 1250 µg/mL Diacetyl: 77 to 215 ug/mL	Exposure to BAL-9141 did not increase the occurrence of chromosomal aberrations. Under similar exposure conditions Diacetyl induced significant increases of the incidences structural aberrations. BAL5788 induced positive results with and without metabolic activation at = 393.2 µg/mL. The positive response was attributed to the cleavage product diacetyl.
Genotoxicity Micronuclei in bone marrow (B169'919)	Mouse; Fullinsdorf Moro Albino (Bone marrow erythrocytes evaluated) 10/dose group	Single IV injection BAL5788	BAL5788: 72 to 450 mg/kg	Toxic/Cytotoxic Effects: Yes; mortality at high dose of 450 mg/kg. Genotoxic Effects: No Under the experimental conditions described in this report BAL-5788 does not induce chromosomal aberrations i*n vivo.*

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Genotoxicity Unschedule DNA synthesis (1003801)	Rat; Han Wistar Hepatocytes evaluated	Single IV injection, BAL5788	BAL5788: 0, 200, 500 mg/kg	Toxic/Cytotoxic Effects: Yes, clinical signs of toxicity at the high dose level of 500 mg/kg.. Genotoxic Effects: No
Fertility and early embryonic development toxicity (BAP00231)	Rat; Crj:CD(SD); 20males/conc. dose group (females not dosed)	Intermittent IV infusion (4 hrs/day); 5% dextrose/BAL5788 plus vehicle	14 days prior to mating, throughout mating, through day 4-5 after end of mating; 0, 175, 250, 360 mg/kg (2mL/kg/hour)	No Observed Adverse Effect Level: F0 Males General Toxicity: 250 mg/kg F0 Males Reproductive Performance: 360 mg/kg Early Embryonic Development: 360 mg/kg NOAEL = 250 and 360 mg/kg/d (18 x clinical b.i.d dose, and 12 x the clinical t.i.d dose) BAL 9141 was excreted into milk samples of rats ~18 –21% of the corresponding maternal plasma concentrations of BAL 9141.
Fertility and early embryonic development toxicity BAP00232	Rat; Crj:CD(SD); 20 females/conc. (males not dosed)	Intermittent IV infusion (4 hrs/day); 5% dextrose/BAL5788 plus vehicle	14 days prior to mating, throughout mating, through day 7 after gestation; 0, 175, 250, 360 mg/kg (2mL/kg/hour)	No Observed Adverse Effect Level: F0 Females General Toxicity: 360 mg/kg F0 Females Reproductive Performance: 360 mg/kg Early Embryonic Development: 360 mg/kg
Fertility and Embryo-fetal development (BAP00173)	Rat; Crj:CD(SD); 29 females/conc.	IV infusion; 4 hrs 5% dextrose/BAL5788 plus vehicle	GD 6-17 (Day of mating = GD 0, Day of C-section = GD 20);-0, 175, 250, 360 mg/kg	No Observed Adverse-Effect Level: F0 Females: 360 mg/kg Embryo/Fetal Development: >360 mg/kg

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Dose Determination Study in pregnant monkeys (BAP00074)	Primate; cynomologus; 3 females	IV infusion (2 hrs/infusion); Reconstitution solution/BAL5788 plus vehicle	3 weeks (one week at each escalating dose); 30, 60, 120 mg/kg (2 mL/kg/hr once daily)	No Observed Effect Level: 30 mg/kg (equivalent to clinical dose)
Fertility and Embryo-fetal development (BAP00229)	Primate; cynomologus; 10 females/conc.	IV infusion (2 hrs/infusion); 5% dextrose/BAL5788 plus vehicle	GD 20-50; 30, 60, 120 mg/kg (2 mL/kg/hr once daily)	No Observed Effect Level: Dams: 60 mg/kg (2 times the clinical dose); Fetuses: 120 mg/kg (4 times the clinical dose)
Pre-and Postnatal development (BAP00640)	Rat; Crj:CD(SD) 24 pregnant females/group; 40 males	IV infusion (4 hrs/day)	GD 6 – GD 21 (F_o females only); 0, 175, 250, 360 mg/kg (2 mL/kg/hr)	No Observed Adverse Effect Level: F0 Females: 175 mg/kg maternal toxicity (~ 6 times clinical dose); 250 mg/kg reproductive toxicity (~8 times clinical dose) F1 Males/Females: 360 mg/kg / 360 mg/kg F2 Litters: 360 mg/kg
Local Tolerance (TOX7588)	Rabbit, Japanese White (Kbl: JW); 3 males/group	Bolus intravenous injection; 5%Dextrose/ BAL5788 plus vehicle	8 days; 2 mg/mL (0.05 mL)/injection site	In the auricles into which BAL5788 was injected, the degree and frequency of inflammation noted in macroscopic examination and histopathology were similar to those in the auricles into which physiological saline was injected. During the administration period, no abnormalities were observed in clinical signs or body weight in any animal.
Local Tolerance (TOX7904)	Rabbit, Japanese White (Kbt: JW); 3 males/group	Bolus intravenous injection; 5%Dextrose/ BAL5788 plus vehicle	8 days (dosing immediately after solution preparation or 30 hours after preparation); 2, 10 mg/mL (0.05 mL)/injection site	No clinical signs of toxicity or body weight effects were observed in any of the BAL5788 treated animals. It was concluded that 2 and 10 mg/mL BAL5788 when prepared immediately prior to dosing or when prepared 30 hours prior to dosing had no irritancy to the auricular veins of rabbits. "Aged" BAL 5788 solution contained high concentrations of BAL 9141 (approximately 35-39%), compared to "fresh" solution (approximately 2-4%). The high concentration of BAL9141 after 30 h is attributed to spontaneous conversion of BAL5788 to BAL9141 in the dosing solution during the storage period (30 h at room temperature).

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Antigenicity Study (B170'669)	Guinea Pig;Hartley; 10 males-test group, 5 males-control group	Intradermal induction: bi-distilled water/BAL5788 plus vehicle and Freunds Complete Adjuvant/physiological saline/BAL5788 plus vehicle Epidermal Induction: bi-distilled water/BAL5788 plus vehicle following pretreatment with 10% sodium lauryl sulfate Challenge: bi-distilled water/BAL5788	Induction: Single injection/test site on Day 1; 0.1 mL of 5% BAL5788 [25 X the clinical concentration] and 0.1 mL of 5% BAL5788 in a 1:1 mixture of Freunds Complete Adjuvant and saline Epidermal Application: patch containing 0.3 mL BAL5788 (25%) applied for 48 hours on Day 8. Challenge: Two weeks following epidermal induction, patch containing 0.2 mL BAL5788 (25%) applied for 24 hours on Day 22.	None of the control or BAL5788 treated animals exhibited skin reactions following challenge with a test article concentration of 25% in bi-distilled water. BAL5788 was not considered to be a skin sensitizer in the Guinea Pig Maximization Model.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Antigenicity Study (TOX7589)	Guinea Pig; Hartley; 5 males/group	Active sensitization: IV; 5% Dextrose/ BAL5788 plus vehicle Active sensitization: Subcutaneous; 5% Dextrose-Freunds Complete Adjuvant (FCA)/BAL5788 plus vehicle) Subcutaneous; 5% Dextrose-Freunds Incomplete Adjuvant (FIA)/BAL5788 plus vehicle) Challenge: Reconstitution Solution/BAL5788 plus vehicle)	IV route: 5 times/week for 3 weeks; 10, 50* mg/kg Subcutaneous route: Once weekly for 3 Weeks; 10, 50 mg/kg Challenge (IV route): Once, 14 days after final sensitization administration; 100 mg/kg Challenge (Passive Cutaneous Sensitization): Intravenous, once 4 hours after passive Sensitization; 0.1 mL/site (Sera from actively sensitized animals diluted 4-64 fold with saline prior to injection.) *Four animals in the 50 mg/kg group were administered the test article at 20 mg/kg for sensitization administrations 5 through 10.	10 mg/kg BAL5788 intravenously: No active systemic anaphylactic reaction was observed in any animal. 10 mg/kg BAL5788 subcutaneously: No active systemic anaphylactic reaction was observed in any animal. 20/50 mg/kg BAL5788 intravenously: Scratching and piloerection were observed in one of five animals. 50 mg/kg BAL5788 with FCA or FIA subcutaneously: Characteristic anaphylactic signs (anxiety, tremor, scratching, piloerection, dyskinesia, dyspnea, and/or convulsion) were observed in all animals, and one animal died. It was concluded that, under the conditions of this study, BAL5788 possesses antigenic potential at $\geq$ 20 mg/kg which is less than than human clinical dose.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Nephrotoxicity Study (1003455)	Rabbit; Chbb:HM, Himalayan; 3 males/group	injection-slow bolus; 0.9% saline/ BAL5788 plus vehicle	Single dose (5mL/kh); Doses (mg/kg): Positive Control - Imipenem - 160 BAL5788 - 160 BAL5788 plus Cilastatin – 160 each	The animals were dosed once on Day 1, clinical pathology evaluations were conducted on Day 2 and the animals were sacrificed on Day 3. Positive Control, Imipenem: demonstrated increased levels of urea, creatinine, urea excretion of NAG, proteinuria and presence of histological changes in kidneys included proximal tubular degeneration/necrosis, cortical mineralization, protein casts in renal cortex and medulla, intracellular inclusions in collecting tubules and papilla. BAL5788: Minimal body weight, red discoloration renal papilla. BAL5788 plus Cilastatin: Slight to moderate swelling of injection site, slight to moderate reduced feces, serum sodium, red discoloration renal papilla, small red foci in lungs. In summary nephrotoxicity was not evident in the BAL5788 treated groups.
Phototoxicity study (1006113)	Balb/c 3T3 Mouse Fibroblast system	In vitro; PBS, 3% DMSO/ BAL9141 plus vehicle	1 hour; 370.6, 529.4, 756.3, 1080.5, 1543.5, 2205, 3150, 4500 µg/mL	BAL9141 absorbed UV light significantly between 240 nm and 400 nm. The test-compound concentration which induced half-maximal inhibition of cell viability (IC50 value) was determined to be > 4500 µg/mL for the non-irradiated cytotoxicity control. For UVA irradiated cells, the IC50 value was calculated as > 4500 µg/mL. The UVA discrimination factor for phototoxicity was 1. Under the conditions tested BAL9141 was shown to be non-phototoxic in vitro on cultured murine fibroblasts after UVA irradiation. Based on these experimental results, it is unlikely that the compound could cause a phototoxic skin reaction in man.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
Phototoxicity (B170'639)	Rat; RORO-n hairless; 6 females/group	Intraperitoneal and intravenous; BAL5788 Formulation not specified	Group 1: 6 daily IP injections followed by single IV injection on day 7; 100 mg/kg* Group 2: single IV dose; 150 mg/kg* Group 3 (placebo): 6 daily IP injections followed by single IV injection on day 7 * as BAL9141	Immediately following the last administration the animals were exposed to increasing UV-light doses of 5, 10, 15, 20, 25, 30, and 35 Joule/cm2. None of the experimental animals presented with cutaneous erythema responses throughout the experiment. BAL5788 did not induce a phototoxic skin reaction in vivo in the hairless rat under the experimental conditions used. The risk that BAL5788 could cause a phototoxic skin response in man is considered to be low if any.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
In Vitro Hemolysis, Plasma Turbidity & Precipitation (1004008)	Dog; Beagle	In vitro dilution; 5% Dextrose /BAL5788 plus vehicle	10 minutes; Hemolysis: 1.56, 3.12, 6.25, 12.5, 25, 40, 50, 60, 80, 100 mg/mL Plasma Turbidity & Precipitation: 12.5, 25, 50, 100 mg/mL (Note: This study used a 13.33% solution of the Prodrug BAL5788, which corresponds to a 10% solution of the active drug, BAL9141.)	No significant hemolysis and plasma turbidity or precipitation was seen at test article concentrations up to 1.25% [12.5 mg/ml (~6.25 times the clinical dose)] of BAL9141, corresponding to 16.6 mg/mL of BAL5788. At higher concentrations of BAL9141, = 2.5% (> 25 mg/mL;12.5 times the clinical dose), corresponding to >33.2 mg/mL of BAL5788, hemolysis up to 7.3% and moderate to marked plasma turbidity and precipitation were observed.

Type of Study	Species/Strain Sex/No. Per Group	Route	Dosage	Principal Effects Observed
In Vitro Hemolysis, Plasma Turbidity & Precipitation (TOX7587)	Human, Rat, Marmoset	In vitro dilution; 0.9% saline/ BAL5788 Lyophilisate plus vehicle	Hemolysis: 3 minutes; 1, 5, 12.5, 25, 50 mg/mL [Volume Ratio (test material:blood): 0.2, 0.4, 0.8] Turbidity and Precipitation: 0.16, 0.5, 1, 2, 3, 5, 10, 30, 60 minutes; 1, 5, 12.5, 25, 50 mg/mL [Volume Ratio (test material:plasma): 0.8]	BAL5788 formulated solution exhibited no significant hemolytic potential at the blood ratios of 0.2, 0.4 and 0.8 (equivalent theoretically to infusion rates of 1.6, 3.2 and 6.4 mL/minute) in human, rat and marmoset blood, at any of the concentrations tested. When mixed with human, rat or marmoset plasma at a ratio of 0.8 (equivalent to an infusion rate of 6.4 mL/minute) BAL5788 exhibited increasing adverse reactions (flocculation, precipitation and coagulation) with increasing BAL5788 concentrations, and with increasing time. In all three species hemolysis, plasma turbidity and precipitation became apparent at the 1.25% or 12.5 mg/mL concentration, and were progressively more pronounced at 2.5%, ~25 mg/mL and 5.0%, ~50 mg/mL, and generally their intensity increased with time. The 5.0% concentration is a 1:2 dilution of plasma. Both human and marmoset plasma behaved similarly, the main adverse reaction was always precipitation, then at higher concentrations, and with increasing time periods, flocculation and coagulation also started to occur, whereas with rat plasma the adverse reaction was always (except in two samples) precipitation. The results of this study indicate that the intravenous administration of BAL5788 formulated in reconstitution solution, whilst causing no significant hemolysis, may cause increasingly significant adverse plasma interactions at infusion solution concentrations of ≥12.5 or 1.25% or 1:80 dilution of plasma (6.25 to 25 times the clinical dose), whichever species is used. The severity of adverse plasma interactions may be exacerbated with increasing infusion volume and/or increasing infusion duration.

REFERENCES

1. Clinical Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Seventh Edition; Approved Standard CLSI Document M7-A7, Vol 26, No. 2, CLSI, Wayne, PA, January, 2006.

2. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests - Ninth Edition; Approved Standard NCCLS Document M2-A9, Vol 23, No. 1, CLSI, Wayne, PA, January, 2006.

PART III: CONSUMER INFORMATION

PrZEFTERA*
ceftobiprole medocaril for Injection

This leaflet is a summary and will not tell you everything about ZEFTERA. Contact your doctor or pharmacist if you have any questions about the drug. This leaflet is Part III of a three-part "Product Monograph" published when ZEFTERA was approved for sale in Canada and is designed specifically for Consumers.

ABOUT THIS MEDICATION

What the medication is used for:
ZEFTERA is used for the treatment of bacterial infections. Your doctor prescribed ZEFTERA because you have a serious infection on or just under your skin, often referred to as a complicated skin and skin structure infection (cSSSI).

What it does:
ZEFTERA is a beta-lactam antibiotic that is believed to work by binding to the penicillin-binding proteins of certain bacteria, helping to stop their growth and reduce the infection.

When it should not be used:
Do not use ZEFTERA if:
- you are allergic to ceftobiprole medocaril or any of its ingredients;
- you are allergic to other β-lactam antibiotics such as penicillins, cephalosporins or carbapenems.

What the medicinal ingredient is:
Ceftobiprole medocaril.

What the nonmedicinal ingredients are:
Citric acid monohydrate and sodium hydroxide.

What dosage forms it comes in:
ZEFTERA is a yellowish or slightly brown coloured powder in a glass vial, ceftobiprole 500mg (as ceftobiprole medocaril). The powder is mixed with water for injections or dextrose 50 mg/ml (5%) solution for injection in the vial to make a solution. The solution is then taken from the vial and added to an infusion bag or other suitable infusion container with sodium chloride 9 mg/ml (0.9%) solution for injection, dextrose 50 mg/ml (5%) solution for injection or Lactated Ringer's injection infusion solution. The medicine is then given intravenously (into a vein).

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal allergic (hypersensitivity) reactions have been reported in patients receiving β-lactam antibiotics (same class as ZEFTERA). Allergic reactions have also been observed with ZEFTERA use. Talk to your doctor if you have had any previous allergic reactions to penicillins, cephalosporins or other allergens.

Before ZEFTERA is administered, it is important that you tell your doctor if you have diarrhea before, during or after your treatment with ZEFTERA. This is because you may have a condition known as colitis (an inflammation of the bowel). Do not take any medicine to treat diarrhoea without first checking with your doctor.

BEFORE ZEFTERA is administered talk to your doctor if:
- You have other infections. While antibiotics including ZEFTERA kill certain bacteria, other bacteria and fungi may continue to grow more than normal. This is called overgrowth. Your doctor will monitor you for overgrowth and treat you if necessary.
- You have kidney disease or if you are having or have had dialysis.
- You are pregnant or are planning to become pregnant.
- You are breast-feeding or if you intend to breast-feed.
- You are taking or have recently taken any other medicines, including medicines you get without a prescription.
- You are under 18 years of age. ZEFTERA should not be given to children or adolescents as there is no experience with the use of ZEFTERA in children.
- You have any allergies to any medicines, including antibiotics
- You have any allergies to this drug or its ingredients
- You have a pre-existing central nervous system disorder as you may experience seizures during treatment with ZEFTERA.

INTERACTIONS WITH THIS MEDICATION

No specific drug interactions with ZEFTERA have been identified yet and no specific drug interaction studies have been conducted. However, the potential for drug interaction with ZEFTERA still exists. Always tell your doctor if you are taking or have recently taken any other medicines, including medicines you get without a prescription.

Co-administration of some cephalosporins (same class as ZEFTERA) with aminoglycosides have caused kidney toxicity. Tell your doctor if you are taking aminoglycosides.

PROPER USE OF THIS MEDICATION

Usual adult dose:
ZEFTERA will always be prepared and given to you by a doctor or another healthcare professional.

The usual dose of ZEFTERA is 500 mg given intravenously (into a vein) over a period of two hours every eight hours, or over a period of an hour every 12 hours, for 7 to 14 days, depending on your condition. Your doctor will decide how long you should be treated. It is very important that you continue to receive ZEFTERA for as long as your doctor prescribes it

In some cases ZEFTERA may be prescribed to patients receiving homecare. The visiting healthcare professional will administer ZEFTERA.

Overdose:
If you are concerned that you may have been given too much ZEFTERA, talk to your doctor or healthcare professional immediately, or contact your local poison control centre.

Missed dose:
If you are concerned that you have missed a dose of ZEFTERA, talk to your doctor or healthcare professional immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ZEFTERA can cause side effects, although not everybody gets them.

A very common side effect reported in more than 10% of patients receiving ZEFTERA is: nausea

Common side effects (1-10%) include: vomiting, diarrhea, indigestion or heartburn, headache, rash, unusual taste, and reactions in and under the skin where the infusion goes into the vein.

Uncommon side effects (≥0.1% - <1%) include: dizziness, itching, low sodium levels in the blood (hyponatremia), fungal infections (these can be in different parts of your body), allergic (hypersensitivity) reactions (including itching and hives), increase in some liver test enzymes.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or healthcare professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	• Inflammation of bowel with diarrhea (*Clostridium difficile* colitis). Symptoms: Diarrhea (may have blood and mucous mixed in it); may be accompanied by stomach cramps)		✓	
	• Serious allergic (hypersensitivity) reactions. Symptoms include: difficulty in breathing, swollen mouth, throat and extremities, severe rash or itching.		✓	

This is not a complete list of side effects. For any unexpected effects while taking ZEFTERA, contact your doctor or pharmacist.

HOW TO STORE IT

ZEFTERA will be stored in the pharmacy, and be prepared by the pharmacist.

For prepared infusion solutions (i.e. reconstituted and diluted):

ZEFTERA infusion solutions will be prepared by the pharmacist. The pharmacist will indicate the exact expiry date and time for the prepared product. The intravenous infusion must be completed before the expiry time.

Once prepared, ZEFTERA infusion solutions may be stored at room temperature (25ºC), or in the refrigerator (2-8ºC). The length of time the solution can be stored depends on the method of preparation, and the dosing regimen you have been prescribed. It is very important that the prepared infusions are stored properly by the health professional.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.janssen-ortho.com
or by contacting the sponsor, Janssen-Ortho Inc., at:
1-800-567-3331

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