PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr ZEVTERA®

Ceftobiprole medocaril powder for injection

500 mg ceftobiprole as 666.6 mg ceftobiprole medocaril sodium per vial

ATC code: J01DI (Other cephalosporins and penems)

Therapeutic Classification: Antibiotic

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# Pr ZEVTERA®

Ceftobiprole medocaril powder for injection

## PART I: HEALTH PROFESSIONAL INFORMATION

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Intravenous | Powder for injection.<br>Each vial contains 500 mg of ceftobiprole (as 666.6 mg ceftobiprole medocaril sodium). | Each vial contains approximately 1.3 mmol (29 mg) of sodium.<br>*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.* |

## INDICATIONS AND CLINICAL USE

ZEVTERA (ceftobiprole medocaril) is 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:

- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
  Caused by: *Staphylococcus aureus* (including MRSA), *Streptococcus pneumoniae*, *Escherichia coli*, and *Klebsiella pneumoniae* (see **DOSAGE AND ADMINISTRATION**).
- Community-acquired pneumonia (CAP)
  Caused by: *Staphylococcus aureus* (including MRSA), *Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, and Haemophilus influenzae* (see **DOSAGE AND ADMINISTRATION**).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZEVTERA and other antibacterial drugs, ZEVTERA 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 ZEVTERA 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 no dose adjustment is necessary in geriatric patients, except in cases of moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION, Recommended dose and dosage adjustment, Renal impairment**).

**Pediatrics (< 18 years of age):**

As the safety and efficacy of ZEVTERA in children aged < 18 years have not yet been established, ZEVTERA is not recommended for use in pediatric patients.

## CONTRAINDICATIONS

ZEVTERA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING**
- Patients who are hypersensitive to the cephalosporin class of antibacterials.
- Patients with immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems).

## WARNINGS AND PRECAUTIONS

**Serious 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 ZEVTERA. Before therapy with ZEVTERA 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 ADEQUATE EMERGENCY MEASURES (see **Hypersensitivity Reactions**).

### Susceptibility / resistance

Prescribing ZEVTERA in the absence of proven or strongly suspected bacterial infection is unlikely to provide benefit the patient and risks development of drug-resistant bacteria.

### General

Superinfection with non-susceptible organisms

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

Clinical efficacy against specific pathogens

Susceptibility to Enterobacteriaceae

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

Efficacy in HAP by multi-drug resistant *S. pneumoniae* (*S. pneumoniae*/MDRSP)

Clinical efficacy data were very limited in MDRSP infected pneumonia subjects in the clinical study involving non-VAP HAP patients. Therefore, ceftobiprole is not recommended in the treatment of HAP caused by this pathogen.

Patients with ventilator-associated pneumonia (VAP)

ZEVTERA has not been shown to be effective in the treatment of patients with VAP. ZEVTERA should not be initiated in patients with VAP.

Limitations of clinical data

There is no experience with ceftobiprole in the treatment of HAP and CAP in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression. Caution is advised when treating such patients.

Precipitation with calcium-containing solutions

Precipitation can occur when ZEVTERA is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, ZEVTERA and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line.

Effects on ability to drive and use machines

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

Dosing above the recommended dose range

There is no clinical experience with ZEVTERA doses higher than the recommended 500 mg administered every eight hours.

Patients on a controlled sodium diet

This medicinal product contains approximately 1.3 mmol (29 mg) sodium per dose. Patients on a controlled sodium diet need to take this into account.

**Endocrine and metabolism**

Potential interference with urine glucose test

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

**Gastrointestinal**

*Clostridium difficile*-associated diarrhea

Antibacterial agent-associated colitis and pseudomembranous colitis have been reported with the use of ZEVTERA and may range in severity from mild to life-threatening. This diagnosis should be considered in patients with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent.

*Clostridium difficile*-associated diarrhea (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*. *Clostridium 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*. Medicinal products that inhibit peristalsis should not be given. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

**Immune**

Hypersensitivity Reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported. In case of severe hypersensitivity reactions, treatment with ZEVTERA must be discontinued immediately.

SERIOUS ACUTE HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS REQUIRE ADEQUATE EMERGENCY MEASURES.

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

**Neurologic**

Patients with pre-existing seizure disorders

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

**Renal**

Renal clearance ($CL_{CR}$) should be measured prior to ceftobiprole dosing.

Due to limited clinical data and an expected increased exposure of ZEVTERA and its metabolite, ZEVTERA should be used with caution in patients with severe renal impairment. Dose adjustments for patients with moderate renal impairment ($CL_{CR}$ 30 to < 50 mL/min) and patients with end-stage renal disease, and prolongation of the infusion duration for patients with supra-normal creatinine clearance ($CL_{CR}$ > 150 mL/min) are discussed in the **DOSAGE AND ADMINISTRATION, Recommended dose and dosage adjustment, Renal impairment** section.

Renal toxicity in animals

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

Potential interference with serum creatinine test

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

***Special populations***

**Pregnant women:** There are no adequate and well-controlled studies with ZEVTERA in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. As no data in exposed human pregnancies are available, ZEVTERA should not be used during pregnancy unless strictly necessary.

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

**Pediatrics (< 18 years of age):** ZEVTERA is not recommended for use in pediatric patients.

**Geriatrics (> 65 years of age):** No dose adjustment is necessary in geriatric patients, except in cases of moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION, Recommended dose and dosage adjustment, Renal impairment**).

## ADVERSE REACTIONS

### Adverse drug reaction overview

The most common adverse drug reactions reported in ≥ 2% in patients treated with ZEVTERA in pneumonia studies are: infusion site reactions (6.5%), hypersensitivity (5.5%), nausea (4.3%), diarrhea (4.2%) and vomiting (3.3%), hyponatremia (2.7%), and phlebitis (2.3%). The majority (82.4%) of adverse events were reported as mild to moderate in severity. Ceftobiprole was discontinued due to an adverse event in 10.3% of subjects compared with 7.3% for all comparators.

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

### Clinical trial and post-marketing adverse drug reactions

Because clinical studies are conducted under very specific conditions, the adverse reaction rates observed in the clinical studies of ZEVTERA may not reflect the rates observed in practice, and should not be compared to the rates in the clinical studies of another drug. Adverse drug reaction information from clinical studies is useful for identifying drug-related adverse events and for approximating rates.

The following adverse reactions were reported during clinical study therapy of community-acquired pneumonia (CAP) and hospital acquired pneumonia (HAP), in which 310 and 386 subjects, respectively, received ceftobiprole at a dose of 500 mg three times daily (Table 1):

**Table 1 Summary of treatment-related adverse reactions by System Organ Class and Preferred Term reported by ≥ 1% of patients in any treatment group in studies CAP-3001 (CAP) and BAP248/307 (HAP)**

| | Ceftobiprole | | Comparator* | |
|---|---|---|---|---|
| | CAP N= 310 (%) | HAP N = 386 (%) | CAP N = 322 (%) | HAP N=386 (%) |
| **Gastrointestinal disorders** | | | | |
| Nausea | 7.1 | 2.1 | 2.2 | 2.1 |
| Vomiting | 5.5 | 1.6 | 1.6 | 0.8 |
| Diarrhea | 5.5 | 3.1 | 4.7 | 6.5 |
| **Hepatobiliary disorders** | | | | |
| ALT increased | 1.6 | 0.8 | 2.5 | 1.6 |
| AST increased | 1.3 | 0.8 | 2.2 | 1.0 |
| **Metabolism and nutrition disorders** | | | | |
| Hyponatremia | 0.6 | 4.4 | 1.2 | 2.6 |
| **Nervous system disorders** | | | | |
| Dysgeusia | 1.9 | 1.3 | 0.3 | 0 |
| Headache | 2.6 | 0.5 | 1.2 | 0.5 |
| Dizziness | 1.3 | 0.3 | 0.3 | 0.5 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash | 1.6 | 0.8 | 0.3 | 1.6 |
| **Vascular disorders** | | | | |
| Phlebitis | 2.6 | 2.1 | 1.6 | 1.3 |

* CAP: ceftriaxone w/wo linezolid; HAP: ceftazidime/linezolid.

The following adverse drug reactions were reported in study CAP 3001 1–3 days after switch from intravenous to oral formulation of ceftobiprole (N=166): diarrhea (1.2%), nausea (0.6%), candidiasis (0.6%), hypocalcemia (0.6%), hyponatremia (0.6%), dizziness (0.6%), and rash (0.6%).

**Less common clinical trial adverse drug reactions reported in pneumonia studies (<1%)**

| | |
|---|---|
| **Blood and lymphatic system:** | leukopenia, anemia, thrombocytosis, thrombocytopenia |
| **Gastrointestinal disorders:** | abdominal pain, dyspepsia |
| **General disorders and administration site conditions:** | peripheral edema, pyrexia |
| **Immune system disorders:** | anaphylaxis |
| **Infections and infestations:** | *Clostridium difficile* colitis |
| **Investigations:** | increased LDH, increased alkaline phosphatase, blood triglycerides increased |
| **Metabolism and nutrition disorders:** | hypokalemia |

| | |
|---|---|
| **Nervous system disorders:** | convulsion, dizziness |
| **Psychiatric disorders:** | insomnia, agitation (including anxiety, panic attacks and nightmares) |
| **Renal and urinary disorders:** | renal failure |
| **Respiratory, thoracic and mediastinal disorders:** | dyspnea, asthma |
| **Skin and subcutaneous tissues disorders:** | pruritus |

**Other adverse drug reactions reported in complicated skin and soft tissue infection studies:**

| | |
|---|---|
| **Investigations:** | blood creatinine increased, blood glucose increased |
| **Blood and lymphatic system:** | eosinophilia |
| **Musculo-skeletal and connective tissue disorders:** | muscle spasms |
| **Nervous system disorders:** | somnolence |
| **Respiratory, thoracic and mediastinal disorders:** | pharyngolaryngeal pain |

**Table 2 Summary of abnormal hematologic and clinical chemistry in any treatment group of CAP and HAP**

| | Ceftobiprole | | Comparator* | |
|---|---|---|---|---|
| | CAP (%) | HAP (%) | CAP (%) | HAP (%) |
| **ALT** | | | | |
| > 3 × ULN and ≤ 5 × ULN | 5.1 | 4.1 | 5.3 | 4.3 |
| > 5 × ULN | 1.7 | 2.8 | 1.3 | 3.4 |
| **AST** | | | | |
| > 3 × ULN and ≤ 5 × ULN | 4.5 | 2.6 | 4.0 | 4.1 |
| > 5 × ULN | 0.3 | 2.3 | 0.7 | 1.6 |
| **Creatinine** | | | | |
| ≥ 50 % increase from baseline | 1.4 | 8.4 | 4.1 | 7.5 |
| ≥ 100 % increase from baseline | 0 | 2.6 | 1.0 | 2.0 |
| **Hyponatremia** | | | | |
| ≤ 129 meq/L | 1.7 | 11.4 | 3.6 | 9.3 |
| ≤ 122 meq/L | 0.3 | 2.5 | 0.3 | 2.4 |

* CAP: ceftriaxone w/wo linezolid; HAP: ceftazidime/linezolid.

**Post marketing adverse reactions**

| | |
|---|---|
| **Blood and lymphatic system:** | agranulocytosis |

## DRUG INTERACTIONS

### Overview

*In vitro* studies have been carried out to investigate potential interactions at the level of CYP enzymes. However, as the concentrations of ceftobiprole used in these studies were limited by solubility, the potential for CYP drug interactions cannot be ruled out.
*In vitro* studies showed that ceftobiprole inhibits OATP1B1 and OATP1B3 with $IC_{50}$s of 67.6 µM and 44.1 µM, respectively. ZEVTERA may increase concentrations of drugs eliminated by OATP1B1 and OATP1B3, such as statins (pitavastin, pravastatin, rosuvastatin), glyburide, and bosentan.

### Drug-drug interactions

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

### Drug-food interactions

Interactions with food have not been established.

### Drug-herb interactions

Interactions with herbal products have not been established.

### Drug-laboratory interactions

Direct antiglobulin test (Coombs test) seroconversion and potential risk of hemolytic anemia: The development of a positive direct antiglobulin test may occur during treatment with a cephalosporin. In clinical studies there was no evidence of hemolytic anemia. However, the possibility that hemolytic anemia may occur in association with ZEVTERA treatment cannot be ruled out. Patients experiencing anemia during or after treatment with ZEVTERA should be investigated for this possibility.

Potential interference with urine glucose test: During treatment with ZEVTERA it is recommended that an enzymatic method to detect glucosuria be used, because of potential interference with tests using the copper reduction technique.

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

## DOSAGE AND ADMINISTRATION

### Dosing considerations

The recommended dose of ZEVTERA is 500 mg administered as a 2-hour intravenous infusion every 8 hours. The usual treatment duration is 4–14 days for CAP, and 7–14 days for HAP, depending on disease severity and the patient's clinical response. For CAP, a switch to an

appropriate oral antibiotic may be considered after completion of at least 3 days of intravenous ceftobiprole medocaril sodium treatment, depending on the patient's clinical response.

**Recommended dose and dosage adjustment**

Renal impairment

In patients with mild renal impairment (i.e., creatinine clearance [$CL_{CR}$] 50 to 80 mL/min), no dosage adjustment is necessary. In patients with moderate renal impairment ($CL_{CR}$ 30 to < 50 mL/min), the recommended dose of ZEVTERA is 500 mg administered every 12 hours as a 2-hour intravenous infusion. In patients with severe renal impairment ($CL_{CR}$ < 30 mL/min), the recommended dose of ZEVTERA is 250 mg administered every 12 hours as a 2-hour intravenous infusion. Due to limited clinical data and an expected increased exposure of ZEVTERA and its metabolite, ZEVTERA should be used with caution in patients with severe renal impairment.

End-stage renal disease requiring dialysis

Ceftobiprole medocaril sodium is hemodialysable. The recommended dose for patients with end-stage renal disease with or without intermittent hemodialysis is 250 mg administered as a 2-hour intravenous infusion once every 24 hours.

Patients with creatinine clearance > 150 mL/min

At start of treatment the prescribing physician should assess the renal function of the patient based on creatinine clearance expressed in mL/minute.

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

Hepatic impairment

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

**Administration**

ZEVTERA must be reconstituted and then further diluted prior to administration by intravenous infusion over a period of 2 hours.

Precipitation can occur when ZEVTERA is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, ZEVTERA and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line.

Step 1. Reconstitution

**Table 3 Reconstituted Solution**

| 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 ceftobiprole |

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

Step 2. Dilution

*Preparation of 500 mg dose of ZEVTERA solution for infusion*

10 mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5–10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 500 mg dose of ZEVTERA.

*Preparation of 250 mg dose of ZEVTERA solution for infusion for patients with severe renal impairment*

Five mL of the reconstituted solution should be withdrawn from the vial and injected into a suitable container (e.g. PVC or PE infusion bags, glass bottles) containing 125 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection, or Lactated Ringer's solution for injection. The infusion solution should be gently inverted 5–10 times to form a homogenous solution. Vigorous agitation should be avoided to prevent foaming. The entire contents of the infusion bag should be infused to administer a 250 mg dose of ZEVTERA.

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

*Disposal*

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

## OVERDOSAGE

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

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

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of action

Ceftobiprole exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs) in susceptible species. In Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), Ceftobiprole binds to PBP2a. Ceftobiprole has demonstrated *in vitr*o activity against strains with divergent *mecA* homologues (*mecC* or *mecA*LGA251).

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

### 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 (500 mg) and supratherapeutic doses (1000 mg).

Convulsions were observed after direct administration into the brain in mice and may be attributed to inhibition of GABA receptor-mediated neurotransmission.

### Pharmacokinetics

Plasma concentrations

The mean pharmacokinetic parameters of ZEVTERA in adults for a single 500 mg dose administered as a 2-hour infusion and multiple 500 mg doses administered every 8 hours as 2-hour infusions are summarized in Table 4. Pharmacokinetic characteristics were similar with single and multiple dose administration in healthy adult subjects.

**Table 4 Mean (standard deviation) ceftobiprole pharmacokinetic parameters in healthy subjects following single and multiple (q8h) intravenous infusions of 500 mg administered over 2 hours**

| Parameter | Single 500-mg dose | Multiple 500-mg doses |
|---|---|---|
| $C_{max}$ (µg/mL) | 29.2 (5.52) | 33.0 (4.83) |
| $AUC_{0-8h}$ (µg*h/mL) | 90.0 (12.4) | 102 (11.9) |
| $t_{1/2}$ (h) | 3.1 (0.3) | 3.3 (0.3) |
| Vss (L) | 21.7 (3.37) | 15.5 (2.33) |
| CLs (L/h) | 4.89 (0.69) | 4.98 (0.58) |
| Amount in urine (% dose) | 83.4% (7.98%) | – |
| %*f*T> MIC=4 µg/mL q8h | – | 84.3% (8.64%) |

Absorption

ZEVTERA 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 liters) approximates extracellular fluid volume in humans.

Metabolism

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

Ceftobiprole undergoes minimal metabolism to the open-ring metabolite, which is microbiologically inactive. Systemic exposure of the open-ring metabolite was considerably lower than for ceftobiprole, accounting for approximately 4% of the parent exposure in subject with a normal renal function.

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

Ceftobiprole protein binding is low (16%) and is not a PgP inhibitor or substrate. The potential for other drugs to interact with ceftobiprole is minimal, since only a small fraction of ceftobiprole is metabolized. Therefore, no relevant drug-drug interactions are anticipated.

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

Excretion

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

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

***Special populations and conditions***

**Pediatrics:** Only limited pharmacokinetic data of ceftobiprole are available in patients below 18 years.
**Geriatrics:** Population pharmacokinetic data showed that age as an independent parameter has no effect on the pharmacokinetics of ceftobiprole. Dosage adjustment is not considered necessary in elderly patients with normal renal function (see DOSAGE AND ADMINISTRATION**, Recommended dose and dosage adjustment, Renal impairment**).

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

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

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

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

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

is recommended in patients with moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION, Recommended dose and dosage adjustment, Renal impairment**).

End-stage renal disease requiring dialysis

AUCs of ceftobiprole and of the microbiologically inactive ring-opened metabolite are substantially increased in patients with end stage renal disease who require 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 ZEVTERA by intravenous infusion, ceftobiprole was demonstrated hemodialysable with an extraction ratio of 0.7.

Patients with creatinine clearance > 150mL/min

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

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

**PK/PD relationship**

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

## STORAGE AND STABILITY

**Storage of vials:**

Vials should be stored under refrigeration (2 °C – 8 °C) in the carton in order to protect from light prior to constitution and should be kept in a safe place out of reach and sight of children.

Shelf life

*Powder vial*

4 years

*After reconstitution*

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

*After dilution*

Chemical, and physical in-use stability data support the total times for reconstitution and infusion (2.67 mg/mL) described in Table 5.

**Table 5 Total time by which reconstitution and infusion (including a 2-hour period of infusion) must be completed**

| Infusion solution diluent | Infusion solutions stored at 25°C | | Infusion solutions stored at 2 °C – 8 °C (refrigerator) |
|---|---|---|---|
| | Protected from light | NOT protected from light* | Protected from light |
| Sodium chloride 9 mg/mL (0.9%) solution for injection | 24 hours | 8 hours | 72 hours |
| Dextrose 50 mg/mL (5%) solution for injection | 12 hours | 8 hours | 72 hours |
| Lactated Ringer's solution for injection | 24 hours | 8 hours | Do not refrigerate |

* Do not expose to direct sunlight

## SPECIAL HANDLING INSTRUCTIONS

Each vial is for single use only. ZEVTERA must be reconstituted and then further diluted prior to infusion (see the **DOSAGE AND ADMINISTRATION** section).
From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The reconstituted and infusion solutions should not be frozen or exposed to direct sunlight.

If the infusion solution is stored in the refrigerator, it should be equilibrated to room temperature prior to administration. The infusion solution does not need to be protected from light during administration. The infusion solution should be prepared and used as defined in **DOSAGE AND ADMINISTRATION** section.

For storage conditions of the reconstituted and/or diluted medicinal product, see the **STORAGE AND STABILITY** section.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Excipients with known effect

Each vial of ZEVTERA contains approximately 1.3 mmol (29 mg) of sodium. The excipients are citric acid monohydrate and sodium hydroxide.

Pharmaceutical Form

ZEVTERA powder for concentrate for solution for infusion is white, yellowish to slightly brownish, cake to broken cake or powder. The pH of the reconstituted solution is between 4.5 and 5.5.

Nature and contents of container

ZEVTERA is supplied as 20 mL clear type I glass vials fitted with a grey bromobutyl elastomeric closure and an aluminum seal with a blue plastic flip-off cap.

A carton contains 10 vials.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug substance

Proper name: ceftobiprole medocaril

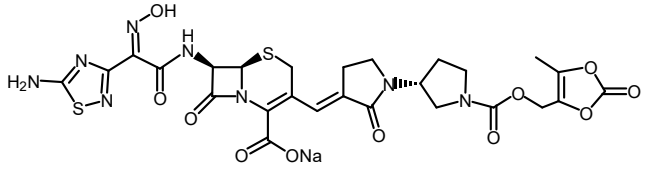
Chemical name: The chemical name for ceftobiprole medocaril (BAL5788) is (6R,7R)-7-[[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetyl]amino]-3-[(E)-[(3'R)-1'-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy]carbonyl]-2-oxo[1,3'-bipyrrolidin]-3-ylidene] methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, monosodium salt.

The chemical name for the active principle ceftobiprole (BAL9141) is (6R,7R)-7-[[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino) acetyl]amino]-3-[(E)-[(3'R)-2-oxo [1,3'-bipyrrolidin]-3-ylidene]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

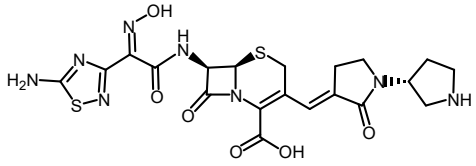
Molecular formula and molecular mass: The molecular formula for the active principle of ceftobiprole (BAL9141) is $C_{20}H_{22}N_8O_6S_2$. The molecular weight for the active principle, ceftobiprole (BAL9141) is 534.57.

The molecular formula for the prodrug, ceftobiprole medocaril (BAL5788) is $C_{26}H_{25}N_8NaO_{11}S_2$. The molecular weight for the prodrug, ceftobiprole medocaril (BAL5788) is 712.64.

Structural formula: *Ceftobiprole medocaril prodrug (BAL5788):*



*Ceftobiprole active principle (BAL9141):*



Physicochemical properties: The prodrug ceftobiprole medocaril (BAL5788) is a water soluble amorphous, yellowish powder. Ceftobiprole medocaril sodium 667 mg corresponds to 500 mg of the active principle ceftobiprole (BAL9141). It is provided as a sterile lyophilized powder that must be constituted and diluted in an appropriate diluent before administration via intravenous infusion. Inactive ingredients are citric acid monohydrate and sodium hydroxide.

### Product characteristics

Ceftobiprole medocaril powder for concentrate for solution for infusion is manufactured by sterile filtration of the ceftobiprole bulk solution and aseptic filling into depyrogenated glass vials. The subsequent lyophilization process results in the final drug product.

## CLINICAL TRIALS

### Study demographics and study design

Hospital acquired pneumonia (HAP)

Study BAP248/307 was a randomized, double-blind, multicenter study of ceftobiprole versus linezolid plus ceftazidime investigating the efficacy and safety of ceftobiprole in subjects with nosocomial pneumonia, including a subset (27%) of patients with VAP.

*Study populations*

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

**Table 6 Summary of patient demographics for study BAP248/307 in hospital acquired pneumonia**

| Trial design | Dosage, route of administration and duration | Study subjects (n = number) | Mean age (Range) | Gender |
|---|---|---|---|---|
| Phase 3, multicentre, randomized, double-blind<br>Aged at least 18 years, with nosocomial pneumonia, microbiological samples suitable for culture and microscopy, APACHE II score ≥ 8 and ≤ 25. | 500 mg ceftobiprole, q8h i.v. as a 2-h infusion for 7 to 14 days + placebo q12h administered as a 1-h infusion, or 600 mg linezolid q12h administered as a 1-h infusion + 2 g ceftazidime q8h as a 2-h infusion for 7 to 14 days.<br>Dose adjustment for renal impairment. | n=781 (ITT) | 61<br>(18–98) | M=521<br>F=260 |

APACHE=Acute Physiology and Chronic Health Evaluation; ITT=intent-to-treat.

*Study results*

The study achieved its primary objective of demonstrating non-inferiority of ceftobiprole compared with ceftazidime plus linezolid for clinical cure rate at the TOC visit. For the secondary efficacy endpoints the outcome for the ceftobiprole and comparator group was similar.

For subjects with HAP (excluding VAP), clinical cure rates were comparable between treatment groups: 154/198 (77.8%) in the ceftobiprole group, and 141/185 (76.2%) in the comparator group. The clinical cure rates in VAP subjects were 20/53 (37.7%) in the ceftobiprole group and 33/59 (55.9%) in the comparator group. The results were similar in the ITT and CE analysis sets.

**Table 7 Main study results in hospital acquired pneumonia (excluding VAP)**

| | Ceftobiprole | | Linezolid/ceftazidime | | | |
|---|---|---|---|---|---|---|
| | **N** | **n (%)** | **N** | **n (%)** | **Diff (%)** | **95% CI [#]** |
| **Enrolled/completed** | 391 | 265 (68) | 390 | 269 (69) | | |
| *Primary endpoint* | | | | | | |
| **Clinical cure at TOC** | | | | | | |
| ITT | | | | | | |
| HAP (excluding VAP) | 287 | 171 (59.6) | 284 | 167 (58.8) | (0.8) | (−7.3; 8.8) |
| Clinically Evaluable | | | | | | |
| HAP (excluding VAP) | 198 | 154 (77.8) | 185 | 141 (76.2) | (1.6) | (−6.9; 10.0) |
| *Secondary endpoints* | | | | | | |
| **Microbiological eradication at TOC** | | | | | | |
| Microbiologically Evaluable | | | | | | |
| HAP (excluding VAP) | 116 | 73 (62.9) | 120 | 81 (67.5) | (−4.6) | (−16.7; 7.6) |
| Microbiological ITT | | | | | | |
| HAP (excluding VAP) | 179 | 87 (48.6) | 181 | 97 (53.6) | (−5.0) | (−15.3; 5.3) |
| **Clinical cure at TOC in subjects with *S. aureus* at baseline** | | | | | | |
| Microbiologically Evaluable | | | | | | |
| HAP (excluding VAP) | 39 | 28 (71.8) | 49 | 36 (73.5) | −1.7 | (−20.4; 17.1) |
| Microbiological ITT | | | | | | |
| HAP (excluding VAP) | 55 | 29 (52.7) | 76 | 43 (56.6) | −3.9 | (−21.1; 13.4) |
| **Clinical relapse at LFU** | | | | | | |
| Clinically Evaluable at the LFU Visit | | | | | | |
| HAP (excluding VAP) | 135 | 5 (3.7) | 128 | 4 (3.1) | (0.6) | (−3.8; 5.0) |
| **30-day pneumonia-specific mortality** | | | | | | |
| ITT | | | | | | |
| HAP (excluding VAP) | 287 | 17 (5.9) | 284 | 16 (5.6) | 0.3 | (−3.5; 4.1) |
| **30-day all-cause mortality** | | | | | | |
| ITT | | | | | | |
| HAP (excluding VAP) | 287 | 48 (16.7) | 284 | 51 (18.0) | -1.2 | (−7.4; 5.0) |

Community-acquired pneumonia (CAP)

Study CAP 3001 was a randomized, double-blind, multicentre study of ceftobiprole versus ceftriaxone with or without linezolid, designed to assess the efficacy and safety of ceftobiprole in adult subjects with CAP requiring hospitalization. A switch from intravenous study drugs to oral therapy (oral cefuroxime axetil; 500 mg every 12 hours) was allowed, after a minimum of 3 days of intravenous therapy, for subjects who met protocol-specified criteria for early improvement and who were candidates for hospital discharge.

*Study population*

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

**Table 8 Summary of patient demographics for study CAP 3001 in community acquired pneumonia**

| Trial design | Dosage, route of administration and duration | Study subjects (n = number) | Mean age (Range) | Gender |
|---|---|---|---|---|
| Phase 3, multicentre, randomized, double-blind<br>Aged at least 18 years, diagnosis of CAP requiring hospitalization and treatment with intravenous antibiotics for at least 72 hours | 500 mg ceftobiprole, q8h as 2-h i.v. infusion 7–14 days + placebo q.d. 0.5-h infusion, or 2 g ceftriaxone q.d. 0.5-h infusion + placebo q8h as a 2-h infusion or 600 mg linezolid q12h as 1-h infusion for 7–14 days. (Linezolid or placebo added if MRSA in CAP isolates prevalent in institution or region or clinically suspected).<br>Dose adjustment for renal impairment | n=638 (ITT) | 55<br>(18–94) | M=366<br>F=272 |

*Study CAP 3001 results*

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

**Table 9 Results of study CAP 3001 in community acquired pneumonia: primary and secondary endpoints**

| | Ceftobiprole | | Ceftriaxone ± linezolid | | | |
|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | Diff (%) | 95% CI* |
| **Enrolled/completed** | 314 | 258 (82) | 324 | 274 (85) | | |
| *Primary endpoint* | | | | | | |
| **Clinical cure at TOC** | | | | | | |
| ITT | 314 | 240 (76.4) | 324 | 257 (79.3) | (−2.9) | (−9.3; 3.6) |
| Clinically Evaluable | 231 | 200 (86.6) | 238 | 208 (87.4) | (−0.8) | (−6.9; 5.3) |
| *Secondary endpoints* | | | | | | |
| **Microbiological eradication at TOC** | | | | | | |
| Microbiologically Evaluable | 68 | 60 (88.2) | 76 | 69 (90.8) | (−2.6) | (−12.6; 7.5) |
| Microbiological ITT | 87 | 70 (80.5) | 97 | 79 (81.4) | (−1.0) | (−12.4; 10.4) |
| **Clinical cure at TOC for subjects with PSI ≥ 91** | | | | | | |
| ITT | 69 | 56 (81.2) | 72 | 56 (77.8) | 3.4 | (−9.9; 16.7) |
| Clinically Evaluable | 51 | 46 (90.2) | 58 | 49 (84.5) | 5.7 | (−6.7; 18.1) |
| **30-day pneumonia-specific mortality** | | | | | | |
| ITT | 314 | 1 (0.3) | 324 | 3 (0.9) | (−0.6) | (−1.8; 0.6) |
| Clinically Evaluable | 231 | 0 | 238 | 2 (0.8) | (−0.8) | (−2.0; 0.3) |

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

Disease severity was assessed using the the PSI score (PORT Risk Class). Twenty-two percent (141/638) of subjects had a PSI score ≥ 91, and 48% (307/638) of patients were in PORT Risk Classes III–V. Non-inferiority of ceftobiprole was demonstrated in these patients.

**Table 10 Results of study CAP 3001: analyses for PORT Risk Classes III–V**

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

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

**Table 11 Microbiological eradication and clinical cure rates by pathogen in HAP (excluding VAP) and CAP patients**

| Pathogen[*] | HAP (excluding VAP) n/N (%) | | CAP n/N (%) | |
|---|---|---|---|---|
| | Ceftobiprole | Linezolid/ ceftazidime | Ceftobiprole | Ceftriaxone (±linezolid) |
| *S. aureus* (MSSA) | | | | |
| Microbiological eradication | 15/20 (75) | 21/30 (70) | 6/6 (100) | 6/6 (100) |
| Clinical cure | 15/20 (75) | 24/30 (80) | 6/6 (100) | 5/6 (83) |
| *S. aureus* (MRSA) | | | | |
| Microbiological eradication | 8/19 (42) | 10/19 (53) | 1/1 (100) | na |
| Clinical cure | 13/19 (68) | 12/19 (63) | 1/1 (100) | na |
| *S. pneumoniae* | | | | |
| Microbiological eradication | 7/7 (100) | 13/14 (93) | 26/28 (93) | 33/36 (92) |
| Clinical cure | 7/7 (100) | 13/14 (93) | 26/28 (93) | 32/36 (89) |
| *H. influenzae* | | | | |
| Microbiological eradication | na | na | 14/16 (88) | 19/21 (90) |
| Clinical cure | na | na | 13/16 (81) | 19/21 (90) |
| *E.coli* | | | | |
| Microbiological eradication | 8/14 (57) | 7/11 (64) | 6/6 (100) | 0/1 (0) |
| Clinical cure | 8/14 (57) | 7/11 (64) | 6/6 (100) | 0/1 (0) |
| *K. pneumoniae* | | | | |
| Microbiological eradication | 10/12 (83) | 15/19 (79) | 4/5 (80) | 7/7 (100) |
| Clinical cure | 11/12 (92) | 15/19 (79) | 4/5 (80) | 7/7 (100) |

## MICROBIOLOGY

Mechanism of Action

Ceftobiprole exerts *in vitro* bactericidal activity over a broad range of pathogens, including both Gram-positive and Gram-negative bacteria, due to its binding to important penicillin-binding proteins (PBPs) such as PBP2a, that confers β-lactam resistance in staphylococci. Ceftobiprole is resistant to hydrolysis by the *S. aureus* PC1 Class A β-lactamase, and is relatively resistant to hydrolysis by many β-lactamases of Class C and Class A Gram-negative bacteria. Like the extended-spectrum cephalosporins, ceftobiprole is hydrolyzed by extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases. The minimum concentration at which 90% of tested strains are inhibited ($MIC_{90}$) against methicillin resistant staphylococci is ≤ 4 μg/mL (MIC range: 0.12 to 8.0 μg/mL), including MRSA from the major epidemic clones. Ceftobiprole has a similar spectrum of activity as cefepime and ceftazidime against *P. aeruginosa* and other Gram-negative organisms. Stable or high-level resistance selection in staphylococci and pneumococci and *Haemophilus influenzae* has been difficult to select *in vitro*.

### Mechanism of resistance

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

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

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

### List of Microorganisms

Clinical efficacy against specific pathogens

Ceftobiprole has been shown to be active against the following bacteria, both in vitro and in clinical infections (see **INDICATIONS AND CLINICAL USE**)

*Hospital-acquired pneumonia (HAP), excluding VAP*

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

*Community-acquired pneumonia (CAP)*

*Staphylococcus aureus* (including MRSA)
*Streptococcus pneumoniae*
*Escherichia coli*
*Klebsiella pneumoniae*
*Haemophilus influenzae*

Antibacterial activity against other relevant pathogens

The following *in vitro* data are available, **but their clinical significance has not been established**. *In vitro* studies suggest that they would be susceptible to ceftobiprole in the absence of acquired mechanisms of resistance. The safety and effectiveness of ceftobiprole in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

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

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

*Chlamydophila (Chlamydia) pneumoniae*
*Burkholderia cepacia complex*
*Mycoplasma pneumoniae*
*Mycobacteria*
*Norcardia spp.*
*Stenotrophomonas maltophilia*

## Susceptibility Test Methods

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in the local hospitals and practice areas should be provided to the physician as periodic resports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

## Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth, and/or agar). The MIC values should be interpreted according to the criteria in Table 12:

**Table 12 Dilution susceptibility interpretive criteria for ceftobiprole**

| Pathogen | MIC breakpoints (mg/L) | | |
|---|---|---|---|
| | Susceptible (≤ S) | Intermediate | Resistant (R >) |
| *Staphylococcus aureus* (including MRSA) | 4 | - | - |
| *Streptococcus pneumoniae* | 0.5 | - | - |
| Enterobacteriaceae | 1 | 2 | 4 |

## Diffusion Techniques

On the basis of regression analyses of antibacterial susceptibility disks loaded with different quantities of ceftobiprole, a ceftobiprole content of 30 µg per disk appeared optimal for disk diffusion studies.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. 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. 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 the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

## Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.

Quality Control ranges for the MIC and disk diffusion zone diameters for the CLSI quality control strains tested are presented in the table below. These ranges were approved by CLSI in June 2005. The data show that the 7 to 9 mm zone diameter ranges for ceftobiprole disk diffusion tests encompass at least 95% of the reported results. Similarly, the 3 to 4 $\log_2$ dilution ranges for ceftobiprole MIC results encompass almost 100% of the reported results.

**Table 13 CLSI-approved QC ranges for ceftobiprole using CLSI MIC and disk diffusion methods**

| Quality Control Organism | Minimum Inhibitory Concentrations (µg/mL) | Disk Diffusion Zone Diameters (mm) |
|---|---|---|
| *S. aureus* ATCC 29213 | 0.12–1 | – |
| *S. aureus* ATCC 25923 | – | 26–34 |
| *E. faecalis* ATCC 29212 | 0.06–0.5 | – |
| *E. coli* ATCC 25922 | 0.03–0.12 | 30–36 |
| *P. aeruginosa* ATCC 27853 | 1–4 | 24–30 |
| *S. pneumoniae* ATCC 49619 | 0.004–0.03 | 33–39 |
| *H. influenzae* ATCC 49247 | 0.12–1 | 28–36 |
| *H. influenzae* ATCC 49766 | 0.015–0.06 | 30–38 |

## TOXICOLOGY

The toxicology program supporting ceftobiprole medocaril (BAL5788) is outlined below.

### Systemic toxicity

Repeated dose studies by intravenous infusion were conducted in the rat (4-week), marmoset (4-week) and dog (2-week). In the rat, daily doses of up to 360 mg/kg/day, given over 4 hours, resulted in minimal to slight cytoplasmic inclusions in the renal proximal tubules (≥250mg/kg/day) which were not associated with any functional changes and were reversible after 4-weeks without treatment. In this study, the no observed adverse effect level (NOAEL) was 360 mg/kg/day (12 × the clinical dose). In the marmoset, daily doses of up to 200 mg/kg/day, given over 4 hours, resulted in slightly increased blood urea nitrogen (BUN) levels and a minimal occurrence of brown pigment in the distal tubular epithelium of the kidneys (200 mg/kg/day), both of which were reversible after 4 weeks without treatment. In the marmoset, the NOAEL was 100 mg/kg/day (3 × the clinical dose). In the dog, daily doses of up to 100 mg/kg/day were given over 30 minutes on Day 1, but were associated with a slight histaminergic reaction, which was attenuated from Day 2 by increasing the infusion duration from to 2 hours. At the end of treatment, eosinophilic droplets were observed in the proximal tubule epithelium of the kidney at ≥ 50 mg/kg/day. In the dog, no NOAEL was established due to slight histaminergic reactions observed at ≥25 mg/kg/day (the lowest dose given).

Subsequent 13-week studies were conducted in the rat, marmoset and dogs by intravenous infusion. In rats, mortality was observed at doses ≥ 250 mg/kg/day due to renal toxicity, characterized by precipitation of drug-like material in the distal part of the nephron, which at lower doses was partially reversible after 4 weeks without treatment. In the rat, the NOAEL was 125 mg/kg/day (4 × the clinical dose). In marmosets, vomiting and reversible renal proximal tubule pigmentation were observed at ≥ 100 mg/kg/day, as well as increases in plasma AST and LDH at 200 mg/kg/day. In the marmoset, NOAELs of 100 and 50 mg/kg/day were established for males and females, respectively (3.3 × and 1.7 × the clinical dose, respectively). In the dog, daily doses of 8 and 32 mg/kg/day were given, although at 32 mg/kg/day the cannula did not remain patent due to infusion site reactions, resulting in the sacrifice of 5/6 dogs, 4 to 11 weeks into the study. There were no additional findings of toxicological importance in these animals. At 8 and 32 mg/kg/day, clinical observations included discoloured urine and a reddening of the skin and mucous membranes (attributed to histamine release). In the dog, the NOAEL was 8 mg/kg/day (approximately 75% less than the clinical dose).

### Carcinogenicity

No lifetime studies in animals have been conducted to evaluate the carcinogenic potential of ceftobiprole.

### Mutagenicity/genotoxicity

The genotoxic potential of the pro-drug ceftobiprole medocaril and its active component ceftobiprole (BAL9141) were examined *in vitro* and *in vivo*.

Ceftobiprole medocaril exhibited clastogenic activity in the ML/TK assay at 750 and 500 µg/mL (cytotoxic concentrations) with and without metabolic activation, respectively, and at 150 µg/mL without metabolic activation, whereas ceftobiprole induced an equivocal effect at 2000 µg/mL. In the HCA assay, ceftobiprole medocaril (but not ceftobiprole) was clastogenic at cytotoxic

concentrations, which is considered attributable to the cleavage product diacetyl. No genotoxic activity was seen with ceftobiprole medocaril *in vivo* at ≤ 500 mg/kg/day in the CHO/HPRT assay, the *in vivo* micronucleus assay in mouse bone marrow, or in an unscheduled DNA synthesis (UDS) assay.

Based on these observations, a genotoxic liability of ceftobiprole medocaril in humans is considered not likely.

**Teratogenicity / impairment of fertility**

Ceftobiprole medocaril 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 or 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 were 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 ceftobiprole medocaril via i.v. infusion (4 h), the NOAEL in dams (F0 generation) was 175 mg/kg (a 6 × multiple of the clinical dose) for maternal toxicity, and 250 mg/kg/day (an 8 × multiple of the clinical dose) for reproductive toxicity. Functional and physical development of the F1 and F2 generations were normal in all groups.

**Juvenile toxicity**

BAL5788 was tested for its effects on juvenile rats (dosing start on Day 1 post-partum) by daily subcutaneous administration for 50 days. Signs of toxicity (e.g., altered activity patterns, increased muscle tone, coordination impairment and retardation of development) were limited to the highest dose (250 mg/kg) and these findings were either fully or partially reversible after a 4-week recovery period. The NOAEL was 100 mg/kg/day. Toxicokinetic investigations showed a decreased $T_{1/2}$ as the dosing progressed, a decrease in exposure, and an increase in renal clearance.

**Other studies**

Infusion site reactions were observed in the 13-week studies in rats and primates. These infusion site reactions were attributable to the physical irritation of the veins by the catheter, the obstruction to the blood flow, and the presence of fibrinous material, all predisposing the veins to irritation from the compound, which ultimately resulted in thrombus formation and the release of emboli. The observed mortality in these studies was attributed to thrombo-embolic changes, which were observed at ≥ 250 mg/kg/day in rats, and in marmosets at ≥ 50 mg/kg/day, where it was preceded by convulsions and a general decline in physical condition.

The potential for antigenicity was observed in guinea pigs after intravenous bolus doses ≥ 20 mg/kg and subcutaneous doses of 50 mg/kg when given in combination with adjuvant, and in dogs as evidenced by the histaminergic response observed in the 2 and 13 week studies.

No hemolysis or precipitation was observed *in vitro* with dog plasma at concentrations ≤ 12.5 mg/mL, although in human, rat and marmoset, plasma turbidity and precipitation were observed at ≥ 12.5 mg/mL.

In local irritation studies in male rabbits, single doses resulted in minimally more irritation compared to saline when given at ≥ 2 mg/mL peri-vascularly, and at 10 mg/mL when given subcutaneously or intramuscularly. There were no effects after inter-arterial administration.

No cephalosporin-specific nephrotoxicity was observed in rabbits, and no phototoxicity was observed *in vitro* (ceftobiprole) or *in vivo* in rats.

## REFERENCES


1. Anderegg T, Jones RN, Sader H, Quality Control Working Group. Quality Control Guidelines for BAL9141 (Ro 63-9141), an investigational cephalosporin, when reference MIC and standardized disk diffusion susceptibility test methods are used. J Clin Microbiol 2004; 42:3356–3358.

2. Azoulay-Dupuis E, Mohler J, Bédos J P, et al. Efficacy of BAL5788, a prodrug of cephalosporin BAL9141, in a mouse model of acute pneumococcal pneumonia. Antimicrob Agents Chemother 2004; 48:1005–1111.

3. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; 18th informational supplement. CLSI Document M100-S18, Jan 2009.

4. Craig A, Andes DR. In vivo pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. Antimicrob Agents Chemother 2008; 52:3492–3496.

5. Farrell DJ, Flamm RK, Sader HS, Jones RN. Ceftobiprole activity against over 60,000 clinical bacterial pathogens isolated in Europe, Turkey, and Israel from 2005 to 2010. Antimicrob Agents Chemother 2010; 58:3882-8.

6. Laohavaleeson S, Tessier PR, Nicolau DP. Pharmacodynamic characterization of ceftobiprole in experimental pneumonia caused by phenotypically diverse Staphylococcus aureus strains. Antimicrob Agents Chemother 2008; 52:2389–2394.

7. Lee DG, Murakami Y, Andes DR, Craig WA. Inoculum effects of ceftobiprole, daptomycin, linezolid, and vancomycin with Staphylococcus aureus and Streptococcus pneumoniae at inocula of 105 and 107 CFU injected into opposite thighs of neutropenic mice. Antimicrob Agents Chemother. 2013; 57:1434–1441.

8. A. E. Muller, N. Punt and J. W. Mouton. Exposure to Ceftobiprole Is Associated with Microbiological Eradication and Clinical Cure in Patients with Nosocomial Pneumonia. Antimicrob. Agents Chemother. 2014, 58(5):2512.

9. Page MGP. Resistance mediated by Penicillin-binding Proteins. In: Bonomo RA, Tolmasky ME (Eds), Enzyme-mediated resistance to antibiotics: mechanisms, dissemination and prospects for inhibition. 2007. ASM Press, Washington DC. 81-99.

10. Rodvold KA, Nicolau DP, Lodise, TP, et al. Identifying exposure targets for treatment of staphylococcal pneumonia with ceftobiprole. Antimicrobial Agents and Chemotherapy 2009;53: 3294–3301.