J Exp Clin Med 2011;3(1):9–16

Contents lists available at ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Ceftobiprole: The First Broad-Spectrum Anti–methicillin-resistant *Staphylococcus aureus* Beta-Lactam

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ARTICLE INFO

Article history:
Received: Jul 10, 2010
Revised: Aug 17, 2010
Accepted: Aug 31, 2010

KEY WORDS:
antibiotic;
ceftobiprole;
cephalosporin;
complicated skin and skin structure infections;
pneumonia

The chemistry, pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, efficacy, safety, and formulary considerations of ceftobiprole are reviewed. Ceftobiprole medocaril is a novel broad-spectrum cephalosporin antibiotic with unique activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and *Enterococcus faecalis*. Spectrum of activity against gram-negative bacteria includes *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*. Ceftobiprole is not active against *Acinetobacter baumannii* and extended-spectrum β-lactamase-producing Enterobacteriaceae. Ceftobiprole at a dosage of 500 mg, infused intravenously over 1 hour every 12 hours, was noninferior to vancomycin in the treatment of complicated skin and skin structure infections (cSSSIs) caused by suspected or documented gram-positive pathogens with cure rates of 93.3% and 93.5%, respectively. Ceftobiprole at a dosage of 500 mg, infused intravenously over 2 hours every 8 hours, was noninferior to the combination of vancomycin and ceftazidime in the treatment of cSSSIs caused by suspected or documented gram-positive or gram-negative pathogens, with cure rates of 90.5% and 90.2%, respectively. Ceftobiprole has also been studied for the treatment of community- and hospital-acquired pneumonia. Clinical trials conducted so far have confirmed the relative safety of ceftobiprole, with nausea, vomiting, and caramel-like taste disturbance being the most common adverse events and allergic reactions the most serious adverse events. Ceftobiprole medocaril is currently approved in Canada and Switzerland for the treatment of cSSSIs. If approved by the food and drug administration, ceftobiprole may represent an attractive option for the treatment of cSSSIs and pneumonias as monotherapy.

1. Introduction

According to the Centers for Disease Control and Prevention, antimicrobial resistance is considered one of the world's most pressing health problems.[1] The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) among hospitalized subjects with *S. aureus* infections is approaching 60%,[2] with increasing prevalence of vancomycin-intermediate *S. aureus*[3] and community-associated MRSA.[4] The incidence of vancomycin-resistant *Enterococcus* infections is around 30%,[2] and the incidence of fluoroquinolone-resistant *Pseudomonas aeruginosa* infections exceeds 30%.[2] There have been only seven systemic antibiotics approved by the Food and Drug Administration (FDA) between 1998 and 2002, five between 2003 and 2007, and two between 2008 and 2010.[2,5] Although it is expected that microorganisms will eventually develop resistance to available antimicrobials, the rate at which they are developing resistance far outweighs our current ability to develop new antimicrobials.[6] For years, vancomycin was considered the gold standard for the treatment of invasive infections caused by MRSA; however, the newly released vancomycin consensus review recommends the use of alternative agents when the minimum inhibitory concentration (MIC) is greater than or equal to 2 mg/L because of unacceptable high rates of clinical failure when vancomycin is used.[7] Currently available alternatives to vancomycin are linezolid, tigecycline, quinupristin-dalfopristin, daptomycin, and the newly approved telavancin.[8,9] Linezolid and tigecycline are bacteriostatic[10,11]; quinupristin-dalfopristin is associated with significant injection site reactions and thrombophlebitis[12]; and daptomycin, although bactericidal, does not achieve a reliable concentration in the lungs.[13] Fortunately, there are new antibiotics in the pipeline directed against gram-positive organisms, such as dalbavancin, oritavancin, and iclaprim,[8] but there are still very few new antibiotics directed against gram-negative organisms.[14]

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† The authors have no conflicts of interest to disclose.

1878-3317/$ – see front matter
doi:10.1016/j.jecm.2010.12.007

Basilea Pharmaceutical AG, Basel, Switzerland, and Johnson & Johnson Pharmaceutical Research and Development LLC, Raritan, New Jersey, developed ceftobiprole medocaril jointly.[15] It is currently the only antibiotic with clinically useful activity against MRSA and *P. aeruginosa*, the only β-lactam with activity against MRSA, and the only cephalosporin with activity against *Enterococcus faecalis*. The drug has been approved in Canada (Zeftera, Janssen-Ortho Inc., Toronto, Ontario) and in Switzerland (Zevtera, Basilea Pharmaceutica Ltd., Basel, Switzerland) for the treatment of complicated skin and soft tissue infections, including diabetic foot infections without concomitant osteomyelitis, and is a promising agent for the treatment of pneumonia. However, ceftobiprole has not been approved yet, neither in the United States nor in the European Union. In fact, the FDA and the European Medicines Agency have issued letters requesting from the manufacturer additional site audits, further studies, and more information.[16]

A review of the literature was performed by searching International Pharmaceutical Abstracts and MEDLINE databases from January 2000 to June 2010 using the search terms ceftobiprole, ceftobiprole medocaril, Ro 63-5788, Ro 63-9141, BAL5788, and BAL9141. Citations in retrieved literature were also reviewed for pertinent information. This article reviews the chemistry, pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, efficacy in humans, safety, and formulary considerations of ceftobiprole.

2. Chemistry and Pharmacology

Ceftobiprole medocaril (also known as Ro 63-5788, BAL5788) is the water-soluble monosodium salt prodrug of ceftobiprole. This prodrug, produced by the chemical modification of a fermentation product, has a molecular formula of $C_{26}H_{25}N_8NaO_{11}S_2$ and a molecular mass of 712.64 (Figure 1).[17] The active drug ceftobiprole (also known as Ro 63-9141, BAL9141) has a molecular formula of $C_{20}H_{22}N_8O_6S_2$ and a molecular mass of 534.27 (Figure 1).[17] After intravenous (IV) administration, ceftobiprole medocaril is rapidly converted to ceftobiprole by plasma esterases.[17,18] The pKa of the carboxylic acid moiety of ceftobiprole is 2.8, and the pKa of the hydroximino functional group is 9.[17]

Ceftobiprole is a novel pyrrolidinone-3-ylidenemethyl cephem that exerts its action by binding to and inactivating penicillin-binding proteins (PBPs), enzymes involved in the terminal stages of bacterial cell wall assembly, and cell wall reshaping during bacterial growth and division.[18,19] Ceftobiprole is specifically designed to have a strong affinity for PBP2a and PBP2x known to confer resistance in staphylococci and pneumococci, respectively.[20,21] In addition, the 7-aminothiazolylhydroxyimino side chain is stable to hydrolysis by the *S. aureus* PC 1 enzyme. Taken together, the inhibition of PBP2a and the stability against beta-lactamases translate into a bactericidal effect against MRSA.[20] Ceftobiprole has an affinity also for PBP1a, PBP2, PBP3, and PBP4 in *Escherchia coli* as well as PBP1a-b, PBP2, PBP3, and PBP4 in *P. aeruginosa*. No affinity was observed for PBP5 and PBP5/6, which are expressed in penicillin-resistant enterococci and *P. aeruginosa*.[22]

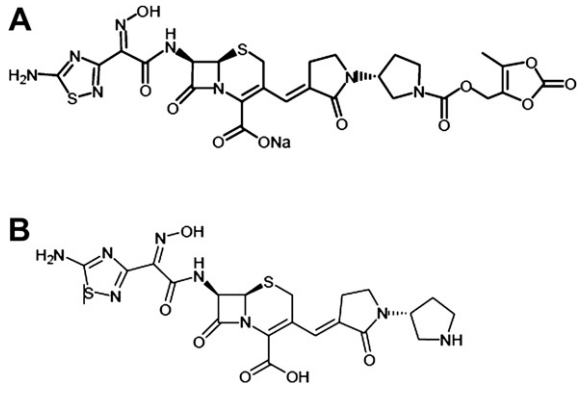

Figure 1 Ceftobiprole medocaril [(A) prodrug] and ceftobiprole [(B) active moiety]. Adapted from Ref. 17.

3. Antimicrobial Activity

3.1. In vitro antimicrobial activity

Ceftobiprole was evaluated *in vitro* against common gram-positive and gram-negative pathogens compared with reference drugs vancomycin, cephalosporins, carbapenems, and fluoroquinolones. It was shown to exhibit an extended spectrum of activity against gram-positive and gram-negative pathogens with stability toward beta-lactamases.[19,23–25]

Ceftobiprole is active against *Staphylococcus epidermidis* and *S. aureus*, including methicillin-susceptible *S. aureus*, community-associated MRSA, hospital-acquired MRSA, vancomycin-intermediate *S. aureus*, and some strains of vancomycin-resistant *S. aureus*. It was consistently active against various strains of staphylococci. The MIC at which 90% of the methicillin-susceptible *S. aureus* and MRSA isolates tested were inhibited (MIC_{90}) were 0.5 and 2 mg/L, respectively.[19,26–34] Ceftobiprole is also active against various streptococci, including *Streptococcus pneumoniae*. It was found to be more potent than cefotaxime against penicillin-resistant *S. pneumoniae* (PRSP), and the MIC_{90} of the PRSP isolates was 0.5 mg/L. Ceftobiprole maintains activity against ceftriaxone-resistant and multidrug-resistant strains of *S. pneumoniae*.[35,36] With regard to enterococci, the activity of ceftobiprole is significantly better than any other commercially available cephalosporins, and the $MIC_{90}$was 2 mg/L for *E.faecalis* isolates; however, ceftobiprole demonstrates poor activity against *Enterococcus faecium* (Table 1).[19,23,25–27,35,36]

Ceftobiprole demonstrates reliable antibacterial activity against *Haemophilus influenzae*; *Moraxella catarrhalis*; and several Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter freundii*, *Serratia marcescens*, and non-derepressed AmpC *Enterobacter cloacae*.[23–25]The MIC at which 50% of the aforementioned gram-negative isolates tested were inhibited (MIC_{50}) was generally less than 0.06 mg/L.[23–25] The MIC_{50} for derepressed AmpC *Enterobacter cloacae* was 8 mg/L. Ceftobiprole also demonstrates activity against *P. aeruginosa* with an MIC_{50} of 2 mg/L for ceftazidime-susceptible strains, but the MIC_{50} rose to 16 mg/L for ceftazidime-nonsusceptible strains.[19,23,25,37] Extended-spectrum beta-lactamase–producing gram-negative rods, *Proteus vulgaris*, *Burkholderia pseudomallei*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophila* are generally resistant to ceftobiprole (Table 2).[19,23–25,38–40]

Gram-positive anaerobic bacteria, such as oral anaerobes, are susceptible to ceftobiprole, but gram-negative anaerobic bacteria, such as *Bacteroides fragilis*, *Porphyromonas* spp., and *Prevotella* spp. have reduced susceptibility to ceftobiprole.[41] The activity of ceftobiprole against *Clostridium* depends on the species. Although *Clostridium perfringens* is susceptible, it seems that *Clostridium difficile* is resistant.[41] None of the published studies have reported any activity against atypical bacteria.

3.2. In vivo antimicrobial activity

The therapeutic efficacy of ceftobiprole has been investigated in several experimental animal models, including endocarditis,[42–44] thigh and lung infections,[45] oesteomyelitis,[46] pneumonia,[47,48] peritonitis,[49] and foreign-body infection.[50]

Table 1 *In vitro* antimicrobial activity of ceftobiprole and reference antibiotics against gram-positive cocci

Staphylococcus aureus	MIC_{90} (mg/L)					
	Ceftobiprole	Cefotaxime	Cefepime	Meropenem	Ciprofloxacin	Vancomycin
MSSA	0.5–1	4	8	0.12	1	2
MRSA	2–4	>64	>32	>32	>8	2

Streptococcus pneumoniae	MIC_{90} (mg/L)						
	Ceftobiprole	Penicillin G	Cefotaxime	Cefepime	Meropenem	Ciprofloxacin	Vancomycin
Penicillin susceptible	0.03	≤0.06	0.06	0.06	0.03	2	1
Penicillin resistant	0.5–2	16	4	4	2	2	0.5

Enterococcus	MIC_{90} (mg/L)						
	Ceftobiprole	Ampicillin	Cefotaxime	Cefepime	Meropenem	Ciprofloxacin	Vancomycin
E. faecalis	2–4	>4	>32	>32	32	>8	>32
E. faecium	8 to >32	8 to >32	>32	>32	>32	>8	>32

Adapted from Refs. 19, 26, 27, 35, and 36.
MIC_{90} = minimum inhibitory concentration for 90% of isolates; MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*.

3.2.1. Endocarditis

The MIC of ceftobiprole for MRSA was 2 mg/L, and it has a bactericidal effect in time–kill curve studies after 24 hours of exposure to two, four, or eight times the MIC. Rats with experimental endocarditis were administered either ceftobiprole to obtain steady-state target levels of 5, 10, and 20 mg/L or 1.2 g of amoxicillin–clavulanate (ratio, 5:1) every 6 hours or 1 g of vancomycin every 12 hours. Ceftobiprole was successful in the treatment of experimental endocarditis because of MRSA at the three targeted steady-state concentrations and sterilized more than 90% of cardiac vegetations ($p < 0.05$ *vs.* all treatment groups). These *in vivo* results with ceftobiprole correlated with the high affinity of the drug for PBP2a and its stability to penicillinase hydrolysis that was observed *in vitro*.[42] A recent study showed that ceftobiprole was superior to vancomycin, daptomycin, and linezolid, in the treatment of a rabbit model of endocarditis caused by MRSA.[44]

3.2.2. Murine thigh and lung infections

Murine thigh and lung infection models in neutropenic and normal mice were used to characterize the *in vivo* pharmacokinetic and pharmacodynamic activities of ceftobiprole against multiple strains of *S. aureus*, including MRSA; *S. pneumoniae*, including PRSP; and gram-negative bacilli. Single doses of ceftobiprole (40 and 160 mg/kg of body weight) were used. The area under the concentration (AUC)–time curve or dose values of 1.8–2.8 mg/L and half-lives of 0.29–0.51 hours were observed for ceftobiprole in mice. Ceftobiprole demonstrated time-dependent killing, and its *in vivo* post-antibiotic effects varied from 3.8 to 4.8 hours for MRSA and from 0 to 0.8 hours for PRSP. The times above MIC ($T > MIC$) were significantly longer ($p < 0.001$) for Enterobacteriaceae (36–45%) than for *S. aureus* (14–28%) and *S. pneumoniae* (15–22%). The drug showed activities in the lung model similar to those in the thigh model.[45]

3.2.3. Osteomyelitis

The efficacies of 4 weeks of treatment with ceftobiprole (40 mg/kg), vancomycin (30 mg/kg), or linezolid (60 mg/kg) were compared, using a rabbit model of MRSA tibial osteomyelitis. After treatment with ceftobiprole, the bacterial titers in all infected left tibiae from evaluable rabbits were below the level of detection, whereas only 73% of infected left tibiae from vancomycin- or linezolid-treated animals had bacterial titers below the level of detection; the mean titers of ceftobiprole were three to five times higher in infected left tibiae than in uninfected right tibiae. These results indicate that ceftobiprole provided effective parenteral treatment of osteomyelitis in this rabbit model.[46]

3.2.4. Pneumonia

The pharmacodynamic profile of ceftobiprole against *S. aureus* strains with a variety of susceptibility phenotypes in an immunocompromised murine pneumonia model was characterized. Pharmacokinetic studies were conducted with infected neutropenic BALB/c mice, and the ceftobiprole concentrations were measured in plasma, epithelial-lining fluid, and lung tissues. Subcutaneous ceftobiprole doses of 2–125 mg/kg of body weight per day were administered. Ceftobiprole exerted maximal antibacterial effects when $fT > MIC$ ranged from 6% to 22%, regardless of the phenotypic profile of resistance to beta-lactam, fluoroquinolone, erythromycin, clindamycin, or tetracycline antibiotics.[48]

Table 2 *In vitro* antimicrobial activity of ceftobiprole and reference antibiotics against gram-negative rods

MIC_{90} (mg/L)					
	Ceftobiprole	Cefotaxime	Cefepime	Meropenem	Ciprofloxacin
Escherichia coli extended-spectrum beta-lactamase (ESBL) negative	0.06	0.12	0.06	0.06	0.12
Escherichia coli ESBL positive	>32	32	8	0.06	0.25
Klebsiella pneumoniae ESBL negative	0.25	≤0.06	0.25	≤0.06	≤0.06
K. pneumoniae ESBL positive	>32	64	16	0.25	>8
ND-AmpC *Enterobacter cloacae*	4	32	0.5	0.12	>2
D-AmpC *E. cloacae*	>32	>64	16	0.25	>8
Ceftazidime-S *Pseudomonas aeuginosa*	8	>64	16	8	>8
Ceftazidime-NS *Pseudomonas aeuginosa*	>32	>64	>32	16	>8
	32	**>32**	**16**	**8**	**2**
Haemophilus influenzae	1	0.25	2	1	0.03
Moraxella catarrhalis	1	0.5	1	≤0.008	0.12

Adapted from Refs. 19, 23–25, and 39.
Ceftazidime-S = ceftazidime susceptible; ceftazidime-NS = ceftazidime nonsusceptible; D-AmpC = derepressed AmpC; MIC_{90} = minimum inhibitory concentration for 90% of isolates; ND-AmpC = non-derepressed AmpC.

3.2.5. Peritonitis

The *in vivo* activity of ceftobiprole against four strains of *E. faecalis*, including beta-lactamase-producing (Bla1) and vancomycin-resistant strains was studied in a murine model of peritonitis. Ceftobiprole doses of 25, 12.5 and 6.25 mg/kg (single doses) and ampicillin doses of 50, 25, 12.5, and 6.25 mg/kg (single and double doses) were administered subcutaneously immediately after bacterial challenge, and the mice were monitored for 96 hours. Ceftobiprole had comparable *in vivo* activity to that of ampicillin against vancomycin-resistant and ampicillin-susceptible strains of *E. faecalis* in the mouse peritonitis model. Ceftobiprole was superior *in vivo* to ampicillin against the Bla1 strain HH22.[49]

4. Resistance

Although there is little clinical evidence of resistance to ceftobiprole, bacteria may develop resistance to beta-lactam by one of the following mechanisms: (1) modification of PBPs, (2) bypassing of normal PBPs, (3) alteration of the outer membranes leading to impermeability, (4) production of beta-lactamases, (5) and ability to pump out (efflux) beta-lactams.[51] It has long been recognized that the modification of PBPs to reduce their affinity for beta-lactams is an important target modification by which gram-positive organisms acquire antibiotic resistance.[52] Banerjee et al[53] demonstrated through molecular modeling data that ceftobiprole resistance can be mediated through mutations in mecA, a gene encoding for PBP2a through three different mechanisms: inhibition of acylation, inhibition of substrate binding, and interference with protein−protein interactions. PBPs may also play a role in resistance to gram-negative rods, namely, *P. aeruginosa*. Through genetic investigation, Moya et al[52] showed that high-level beta-lactam resistance *in vitro*, *in vivo*, and in a clinical setting, is driven by the inactivation of the dacB-encoded nonessential PBP4, which behaves in a manner so as to trap target beta-lactam. Ceftobiprole, like cefepime, is an atypical beta-lactam that is a substrate for the MexXY efflux pump, and *P. aeruginosa* may develop resistance to ceftobiprole through overexperession of Mex pumps.[54]

5. Pharmacokinetics and Pharmacodynamics

The safety and pharmacokinetics of ceftobiprole were investigated in a double-blind, single-ascending-dose study with 40 healthy male subjects.[18,55] The subjects were randomized to receive either placebo ($n = 2$ subjects per dose) or ceftobiprole ($n = 6$ subjects per dose) as a 200-mL IV infusion over 30 minutes. The ceftobiprole doses used were 125, 250, 500, 750, and 1000 mg. The maximum concentration of drug in serum and the area under the concentration−time curve for ceftobiprole were dose proportional over the dosing range. The elimination half-life of ceftobiprole was about 3 hours. More than 70% of the administered dose was excreted as ceftobiprole in the urine, and almost no prodrug was detected. Conversion of ceftobiprole medocaril to the active form ceftobiprole is very rapid in human plasma (38 seconds). The volume of distribution at steady state was equal to the volume of the adult extracellular water compartment, and the renal clearance of free drug corresponded to the normal glomerular filtration rate for adults (Table 3).[18,56] The protein binding of ceftobiprole was determined to be 16% and was independent of concentration across the range of 0.5−100 μg/mL.[55] Ceftobiprole is primarily bound to albumin (6.5−11.5%) and alpha-1-acid glycoprotein (4.8−6.8%). It achieves sufficient drug penetration capabilities into the skeletal muscle and the subcutaneous adipose tissue and is, therefore, clinically useful in the treatment of cSSSIs.[57] After a 30-minute infusion of 750 mg, the mean plasma ceftobiprole concentrations exceeded the MIC at which 100% of MRSA isolates are inhibited (4 mg/L) for approximately 7 hours or at 58% of a 12-hour dosing interval. In the multiple-dose study, 16 healthy male volunteers were randomized to receive either ceftobiprole at 500 or 750 mg ($n = 6$ subjects per dose) or placebo ($n = 2$ subjects per dose). The doses were given as 200-mL infusions over 30 minutes once daily on Days 1 and 8 and twice daily on Days 2−7.[56] The results of pharmacokinetic analyses agreed well with the data reported from a previous single-ascending-dose study.[18] After multiple infusions of 750 mg, the mean concentrations of ceftobiprole in plasma exceeded the MIC at which 100% of MRSA isolates are inhibited (4 mg/L) for approximately 7−9 hours, corresponding to 58−75% of a 12-hour dosing interval.

Like all beta-lactam antibiotics, ceftobiprole exhibits time-dependent bacterial killing. A relationship between $\%T > \text{MIC}$ and clinical cure was demonstrated in the treatment of cSSSIs.[58] Gram-negative bacteria require higher drug targets than gram-positive bacteria, and higher doses or more frequent dosing is often needed for gram-negative bacteria.[59−61] The $fT > \text{MIC}$ for a bactericidal effect is 60%, and the $fT > \text{MIC}$ for a bacteriostatic effect is 40%. The pharmacokinetics of ceftobiprole in critically ill subjects is currently under investigation.[62]

6. Efficacy in Humans

6.1. Clinical trials

Two randomized, multinational, double-blind, noninferiority (10% margin) clinical trials were conducted to assess the efficacy and safety of ceftobiprole in the treatment of adults with cSSSIs. In both trials, cSSSIs were defined as infections involving subcutaneous tissues or requiring surgical intervention and IV therapy, along with at least one of the following characteristics: onset of infection within 30 days after surgery or trauma, onset of abscess during the 7 days before enrollment, and onset of cellulitis during the 7 days before enrollment. Table 4 summarizes these clinical trials.[63,64]

Table 3 Pharmacokinetic parameters of ceftobiprole in healthy subjects

Dose (mg)	Area under the curve $(AUC)_{0-\infty}$ (mg/L·hr)	C_{max} (mg/L)	$T_{1/2,\beta}$ (hr)	Volume of distribution at steady-state (Vss) (L)	Clearance (CL) (L/hr)	Renal clearance (CL_R) (L/hr)
Single dose						
125	20.3 (2.82)	9.87 (0.78)	2.84 (0.21)	17.9 (2)	6.27 (0.97)	4.6 (0.38)
250	43.7 (5.99)	19.5 (2.75)	3.42 (0.29)	17.8 (3.11)	5.81 (0.84)	4.35 (0.57)
500	76.6 (3.88)	35.5 (6.79)	3.44 (0.3)	19.8 (1.95)	6.54 (0.34)	5.07 (0.22)
750	135 (27.6)	59.6 (10.7)	3.47 (0.37)	18.4 (2.63)	5.74 (1.13)	4.08 (0.75)
1000	151 (9.04)	72.2 (8.78)	3.25 (0.2)	18.9 (2.31)	6.64 (0.41)	4.16 (0.57)
Multiple dose						
500 (Day 1)	101 (9.04)	40.6 (7.38)	3.63 (0.48)	16.4 (2.11)	4.99 (0.46)	4.12 (0.75)
500 (Day 8)	108 (22.2)	44.2 (10.8)	4.04 (0.31)	16.7 (3.58)	5.05 (0.95)	4.47 (1.07)
750 (Day 1)	156 (19.3)	60.7 (4.55)	3.64 (0.32)	16.3 (1.82)	4.85 (0.57)	4.05 (0.47)
750 (Day 8)	165 (12.8)	60.6 (9.99)	4.11 (0.41)	16.1 (2.2)	4.84 (0.34)	4.09 (0.6)

Adapted from Refs. 18 and 56.

Table 4 Ceftobiprole clinical trials in complicated skin and skin structure infections (cSSSIs)

Reference	Design	Duration (days)	Inclusion criteria	Exclusion criteria	Dose	CE		cMITT		ME		mMITT	
						No. of patients or subjects (pts)	Clinical cure % (difference, 95% CI)	No. of pts	Clinical cure % (difference, 95% CI)	No. of pts	Clinical cure % (difference, 95% CI)	No. of pts	Clinical cure % (difference, 95% CI)
Noel et al[63]	MC, MN, R, DB, NI, ITT	7–14	≥18 yr of age, documented or suspected GPB	History of allergic reaction or intolerability to either cephalosporins or vancomycin, severe renal impairment, hepatic impairment, pregnant or lactating women, subjects with neutropenia, HIV subjects with CD4 counts $<0.2 \times 10^9$/L, diabetic foot infections, osteomyelitis, infections associated with animal or human bites	CFB: 500 mg IV every 12 hours (q12h), through a 60-min infusion	282	93.3	397	77.8	226	94.2	312	NR
					VCN: 1000 mg q12h, through a 60-min infusion	277	93.5 (−4.4, 3.9)	387	77.5 (−5.5, 6.1)	217	93.5 (−3.8, 5.2)	301	NR
Noel et al[64]	MC, MN, R, DB, NI, ITT	7–14	≥18 yr of age, documented or suspected GPB or GNB	History of allergic reaction or intolerability to either cephalosporins or vancomycin, severe renal impairment, hepatic impairment, pregnant or lactating women, subjects with neutropenia, HIV subjects with CD4 counts $<0.2 \times 10^9$/L, foreign-body infection, osteomyelitis, critical limb ischemia, septic arthritis	CFB: 500 mg IV every 8 hours (q8h), through a 120-min infusion to optimize time > MIC	485	90.5	547	81.9	391	88	434	NR
					VCN: 1000 mg IV q12h, through a 60-min infusion CTZ: 1000 mg IV q8h, through a 120-min infusion	244	90.2 (−4.2, 4.9)	281	80.8 (−4.5, 6.7)	199	89 (−6.4, 4.5)	224	NR

Adapted from Refs. 63 and 64.
CE = clinically evaluable; CFB = ceftobiprole; CTZ = ceftazidime; cMITT = clinical modified intent to treat; cSSSIs = complicated skin and skin structure infections; DB = double blind; GNB = gram-negative bacteria; GPB = gram-positive bacteria; HIV = human immunodeficiency virus; ITT = intent to treat; MC = multicenter; ME = Microbiologically evaluable; MIC = minimum inhibitory concentration; mMITT = microbiological modified intent to treat; MN = multinational; NI = noninferiority; NR = not reported; R = randomized; VCN = vancomycin.

The Noel et al[63] trial was designed to compare the efficacy of ceftobiprole at a dosage of 500 mg IV every 12 hours, infused over an hour, with that of vancomycin at a dosage of 1000 mg IV every 12 hours, infused over an hour, in subjects with cSSSIs caused by suspected or documented gram-positive bacteria. The study drug was given for 7–14 days, and the use of metronidazole or aztreonam was allowed at the discretion of clinicians if anaerobic or gram-negative bacteria were suspected. The cure rates for subjects with MRSA infections were 91.8% (56/61) in the ceftobiprole arm and 90.0% (54/60) in the vancomycin arm [95% confidence interval (CI): −8.4%, 12.1%]. The authors concluded that ceftobiprole was noninferior to vancomycin in the treatment of cSSSIs caused by gram-positive bacteria.[63]

The Noel et al trial[64] was designed to compare the efficacy of ceftobiprole at a dosage of 500 mg IV every 8 hours, infused over 2 hours, with that of a combination of vancomycin at a dosage of 1000 mg IV every 12 hours, infused over an hour, and ceftazidime at a dosage of 1000 mg IV every 8 hours, infused over 2 hours, in subjects with a broad range of cSSSIs caused by suspected or documented gram-positive or gram-negative bacteria. Inclusion criteria were extended to include subjects with diabetic foot infections but without concomitant osteomyelitis. The study drug was given for 7–14 days, and the use of metronidazole was allowed at the discretion of the clinicians if anaerobic bacteria were suspected. The cure rates of subjects with gram-positive bacteria infections were 91.8% (292/318) in the ceftobiprole arm and 90.3% (149/165) in the comparative arm (95% CI: −3.6%, 7.6%). More specifically, the cure rates of subjects with MRSA infections were 89.7% (78/87) in the ceftobiprole arm and 86.1% (31/36) in the comparative arm (95% CI: −8.0%, 19.7%). The cure rates of subjects with gram-negative bacteria infections were 87.9% (109/124) in the ceftobiprole arm and 89.7% (61/68) in the comparative arm (95% CI: −11.0%, 9.1%). More specifically, the cure rates for subjects with *E. coli* and *P. aeruginosa* infections were 89.2% (33/37) and 86.7% (26/30), respectively, in the ceftobiprole arm, and 92.3% (24/26) and 100% (9/9), respectively, in the comparative arm (95% CI: −19.0%, 15.9% and −30.2%, 18.5%, respectively). The authors concluded that ceftobiprole monotherapy was noninferior to vancomycin plus ceftazidime in the treatment of cSSSIs caused by gram-positive or gram-negative bacteria. However, there were more *P. aeruginosa* isolates in the ceftobiprole group (30 isolates) than those in the comparative group (9 isolates), and the study was not powered to detect differences among various isolates.[64]

Limitations of the currently published cSSSI studies include the exclusion of critically ill subjects, subjects with osteomyelitis or septic arthritis, subjects with foreign-body infection, and subjects with significant hepatic or renal impairment. In addition, the studies were supported by the manufacturer of ceftobiprole and the principle investigator, and some authors are full-time employees of the manufacturer.

Ceftobiprole has also been studied in community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).[62,65–67] A randomized, double-blind, noninferiority clinical trial was conducted to compare the safety and efficacy of ceftobiprole 500 mg IV every 8 hours with that of ceftriaxone 2000 mg IV every 24 hours with or without linezolid 600 mg IV every 12 hours in the treatment of subjects hospitalized for CAP. Patients were stratified before randomization based on the pneumonia severity index (≤90; ≥91) and the need to add linezolid to ceftriaxone therapy. Among the clinically evaluable subjects, the cure rates were 86.7% (202/233) in the ceftobiprole arm and 87.6% (212/242) in the comparative arm. Among the intention-to-treat subjects, the cure rates were 77.4% (254/328) in the ceftobiprole arm and 80.2% (271/338) in the comparative arm. The cure rates in subjects with *S. pneumoniae* infection were 93% (26/28) with ceftobiprole and 89% (32/36) with the comparative arm. The cure rates in subjects with *S. aureus* infections were 100% (7/7) with ceftobiprole and 83% (5/6) in the comparative arm. The authors concluded that ceftobiprole was noninferior to ceftriaxone with or without linezolid in the treatment of hospitalized subjects with CAP. CIs were not provided in the abstract, and the investigators excluded subjects with suspected atypical bacteria.[65,67]

A double-blind, multicentered, noninferiority clinical trial was conducted to compare the safety and efficacy of ceftobiprole 500 mg IV every 8 hours with those of ceftazidime 2000 mg IV every 8 hours plus linezolid 600 mg IV every 12 hours in the treatment of HAP. Patients were stratified according to the Acute Physiology and Chronic Health Evaluation II score (<19; ≥20) and the ventilator-associated pneumonia (VAP) status. Patients were assessed 10–14 days after completing therapy. Among the clinically evaluable subjects, the cure rates were 69.3% (174/251) in the ceftobiprole arm and 71.6% (179/250) in the comparative arm (95% CI: −10.3%, 5.7%). More specifically, among VAP subjects, the cure rates were 38.5% (20/52) with ceftobiprole and 56.7% (34/60) with the comparative group (95% CI: −36.4%, 0.0%). Among the intention-to-treat subjects, the cure rates were 49.9% (195/391) in the ceftobiprole arm and 52.8% (206/390) in the comparative arm (95% CI: −10.0%, 4.1%). More specifically, among the VAP subjects, the cure rates were 23.5% (24/102) with ceftobiprole and 36.2% (38/105) with the comparative group. The authors concluded that ceftobiprole was noninferior to ceftazidime and linezolid in the treatment of HAP; however, lower cure rates were evident in the ceftobiprole-treated VAP subjects, and factors associated with these lower rates were not established.[66]

Ceftobiprole has also been studied in hospitalized subjects with *S. aureus* bacteremia and in subjects with febrile neutropenia.[62] To our knowledge, none of these studies have been published.

6.2. Safety

6.2.1. Adverse events

The most common side effects observed during cSSSI clinical trials were of gastrointestinal origin, with nausea (11–14%), dysgeusia and caramel-like taste disturbances (8%), vomiting (6–7%), diarrhea (5–8%), and headache (7–8%) being the most common adverse events.[63,64,68] Hyponatremia leading to drug discontinuation (0.3%) has been rarely observed in clinical trials. Nonetheless, ceftobiprole should be used with caution in subjects at risk of hyponatremia.[17]

Like all cephalosporins, ceftobiprole carries the risk of rash and hypersensitivity reactions and should generally be avoided in subjects with a history of allergic reactions to cephalosporins or severe allergic reactions to penicillins. Rash (2%), pruritus (3%), and hypersensitivity reactions (5%) were among the reasons that led to the discontinuation of the drug during clinical trials. Ceftobiprole also carries a small risk of seizures, particularly in subjects with preexisting central nervous system disorders and renal impairment (<1%).[17,63,64] As with all antibiotics, there is a risk of *C. difficile* infection associated with the use of ceftobiprole.

6.2.2. Drug interactions

Because protein binding of ceftobiprole is low (16%) and independent of concentration, displacement interactions are not anticipated. Ceftobiprole is not extensively metabolized and does not induce cytochrome (CYP) isoenzymes; therefore, metabolic drug–drug interactions are not anticipated. It is neither a substrate nor an inhibitor of *p*-glycoprotein; consequently, transport-related interactions are not anticipated. Ceftobiprole is primarily excreted by glomerular filtration without tubular secretion or reabsorption. Hence, the overall likelihood of drug–drug interactions is minimal.[55] As with other antibiotics, potential drug–drug interactions include a possible increase in INR when used with warfarin and a decrease in the efficacy of live attenuated bacterial vaccines, such as the oral typhoid vaccine (Ty21a).

7. Dosing and Administration

According to the Canadian product monograph,[17] the recommended regimen for the treatment of cSSSIs because of gram-positive pathogens is 500 mg IV every 12 hours, infused over 60 minutes, for 7–14 days, and for the treatment of cSSSI because of gram-negative pathogens or polymicrobial pathogens, it is 500 mg IV every 8 hours, infused over 120 minutes, for 7–14 days. The recommended regimen for the treatment of non-limb-threatening diabetic foot infections without concomitant osteomyelitis is 500 mg IV every 8 hours, infused over 120 minutes, for 7–14 days.

7.1. Patients with renal impairment

It has been observed that ceftobiprole plasma concentration increases with decreasing renal function. Although dosing adjustment is unnecessary in mild renal impairment (creatinine clearance (CrCl): 50–80 mL/min), it is required in subjects with moderate renal impairment (CrCl: 30–50 mL/min). In these subjects, the infusion time is extended to a 120-minute infusion of 500 mg ceftobiprole every 12 hours. Severe renal impairment (CrCl: <30 mL/min) requires the dose to be reduced to 250 mg administered every 12 hours as a 120-minute IV infusion. Data on dosing requirements for subjects with end-stage renal disease (CrCl: <10 mL/min) or for subjects on dialysis are not available.[17,55]

7.2. Patients with hepatic impairment

No dosage adjustment is necessary in subjects with hepatic impairment as ceftobiprole undergoes minimal hepatic metabolism and is eliminated predominantly by the kidney.[17,55]

7.3. Gender

The systemic exposure (Cmax and area under the curve (AUC)) of a 750-mg dose of ceftobiprole infused over 30 minutes has been observed to be similar in males and females; therefore, dosing adjustments based on gender are not required.[17,55]

Currently, ceftobiprole medocaril is supplied in Canada as a sterile lyophilized powder to be reconstituted with water for injection or 5% dextrose solution for injection. Ceftobiprole vials should be stored refrigerated at 2–8°C in the carton to protect from light before constitution. Once reconstituted, ceftobiprole is chemically, physically, and microbiologically stable for an hour at room temperature (25°C) and 24-hour refrigeration (2–8°C).[17]

Seventy drugs were evaluated for compatibility with 2 mg/mL ceftobiprole in 5% dextrose injection, 0.9% sodium chloride injection, and lactated Ringer's injection. Thirty-one were found to be compatible and 32 were found to be incompatible in all three of the infusion solutions. For seven of the drugs, compatibility was dependent on which infusion solution was used.[69] Ceftobiprole should not be simultaneously administered through a Y site with drugs with which it was shown to be incompatible.

8. Formulary Considerations

Ceftobiprole represents the newest addition to the arsenal of β-lactam antibiotics. It is a novel cephalosporin with a broad spectrum of activity against gram-positive cocci, including MRSA, PRSP, *E. faecalis*, and against gram-negative bacilli, including *E. coli*, *P. mirabilis*, *E. cloacae*, *K. pneumoniae*, and *P. aeruginosa*. It is inactive against *Enterococcus faecium*, extended-spectrum beta-lactamase-producing Enterobacteriaceae, *A. baumannii*, and *Bacteroides fragilis*. Ceftobiprole has a favorable safety profile and a low potential for drug–drug interactions. If approved by the FDA and the European Medicines Agency, ceftobiprole may replace the use of combination therapy in the empirical treatment of subjects with cSSSIs, particularly when both gram-positive and gram-negative bacteria are suspected, which is the case in subjects with diabetes. Ceftobiprole may also replace the use of combination therapy in the empirical treatment of subjects with pneumonias, particularly when atypical organisms are not suspected, such as that in subjects with HAP. Additional studies are underway to determine the much needed role of ceftobiprole in the treatment of bacteremia, endocarditis, and respiratory tract infections. Recently, the role of vancomycin as the gold standard for the treatment of MRSA infections has been questioned, and because daptomycin cannot be used for the treatment of pneumonia because of low penetration into the lungs and tigecycline and linezolid are bacteriostatic, ceftobiprole, because of its bactericidal activity, may emerge as an attractive option for the treatment of various infections in an era where the prevalence of community-associated and hospital-acquired MRSA is at record high level. However, caution should be exercised when using an antibiotic with a broad-spectrum of activity because of its ability to induce resistance and streamlining according to culture and sensitivity should be highly encouraged. If selected to be on formulary, medical and nursing staff should be educated on the two different dosing regimens of ceftobiprole. A 1-hour infusion of 500 mg every 12 hours is needed for gram-positive infection and a 2-hour infusion of 500 mg every 8 hours is needed for gram-negative or polymicrobial infection. In addition, dose adjustment is needed in subjects with renal impairment.

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