

Ceftobiprole: A novel, broad-spectrum cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*

DANIEL G. DAUNER, ROBERT E. NELSON, AND DONNA C. TAKETA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is endemic in hospitals and has emerged in the community.^{1,2} The widespread use of vancomycin, an effective antibiotic against MRSA, has led to the development of isolates with reduced susceptibility. Rare cases of vancomycin-resistant *S. aureus* infections have been reported in the medical literature and are of particular concern.

Several new agents with gram-positive activity, including daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline, are available on the market.^{3,4} However, some of these agents, such as linezolid and tigecycline, are bacteriostatic rather than bactericidal.^{5,6} Of the new agents listed above, only tigecycline has a broad spectrum of activity against both gram-positive and gram-negative pathogens, restricting the use of the other agents to combination therapy.⁶ Ceftobiprole is a novel, broad-spectrum,

Purpose. The pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, clinical efficacy, safety, and place in therapy of ceftobiprole are reviewed.

Summary. Ceftobiprole, a novel, broad-spectrum, parenteral cephalosporin, inhibits the cell-wall synthesis of penicillin-binding proteins (PBPs) PBP2a and PBP2x, responsible for the resistance in staphylococci and pneumococci, respectively. Ceftobiprole has good activity against gram-positive aerobes and anaerobes, and its activity against gram-negative aerobes and anaerobes is species dependent. Ceftobiprole is relatively inactive against *Acinetobacter* species. Its ability to bind relevant PBPs of resistant gram-positive and gram-negative bacteria indicates its potential use in the treatment of hospital-acquired pneumonia and complicated skin and skin-structure infections (cSSSIs). Ceftobiprole is primarily excreted unchanged by the kidneys and exhibits linear pharmacokinetics. The half-life of the drug is approximately 3–4 hours. It exhibits minimal plasma protein binding (16%). Ceftobiprole does not inhibit the cytochrome P-450 isoenzyme system, so the possibility of drug–drug interactions

is low. The drug has not been approved for use in the United States but has been approved in Canada and elsewhere. Ceftobiprole is currently undergoing Phase III clinical trials and has demonstrated activity against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. Completed Phase III trials used i.v. dosages of 500 mg every 8–12 hours. The most commonly observed adverse effects of ceftobiprole included headache and gastrointestinal upset.

Conclusion. Ceftobiprole is a novel, broad-spectrum, parenteral cephalosporin undergoing Phase III clinical trials. Its broad spectrum of activity makes it a candidate for monotherapy of cSSSIs and pneumonias that have required combination therapy in the past.

Index terms: Binding; Ceftobiprole; Cephalosporins; Dosage schedule; Drug interactions; Excretion; Half life; Mechanism of action; Methicillin; Penicillins; Pharmacodynamics; Pharmacokinetics; Resistance; Spectrum microbial; Staphylococcal infections; *Staphylococcus aureus*; Toxicity

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DANIEL G. DAUNER, PHARM.D., M.S.P.H., BCPS, is Pharmacy Clinical Coordinator, St. Luke's Hospital, Duluth, MN, and Assistant Professor, College of Pharmacy, University of Minnesota—Duluth, Duluth. ROBERT E. NELSON, PHARM.D., BCPS (AQ-Infectious Disease), is Clinical Pharmacy Manager, MeritCare Hospital, Fargo, ND, and Assistant Professor, College of Pharmacy, Nursing, and Allied Sciences, North Dakota State University, Fargo. DONNA C. TAKETA is pharmacy student, College of Pharmacy, University of Minnesota, Minneapolis.

Address correspondence to Dr. Dauner at St. Luke's Hospital,

University of Minnesota, 915 East First Street, Duluth, MN 55805 (ddauner@slhduluth.com).

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β -lactamase-stable, i.v. cephalosporin with a strong affinity for the penicillin-binding proteins (PBPs) PBP2a and PBP2x, responsible for resistance in staphylococci and pneumococci, respectively.^{7,8} Cefotibiprole also can bind to relevant PBPs of resistant gram-positive and gram-negative bacteria and has a low ability to select for resistance.^{7,8} Cefotibiprole is not approved for use in the United States.

This article reviews the pharmacology, antimicrobial activity, pharmacokinetics, pharmacodynamics, clinical efficacy, safety, and place in therapy of cefotibiprole.

Chemistry and pharmacology

Cefotibiprole is a novel pyrrolidino-3-ylidene-methyl cephalosporin.^{8,9} It is administered as cefotibiprole medocaril, a water-soluble prodrug that allows for i.v. administration.¹⁰ After i.v. administration, cefotibiprole medocaril is rapidly converted to cefotibiprole. It is thought that type-A esterases in the plasma are involved in this conversion, which takes approximately 38 seconds in humans.¹⁰ Only 0.68% of the dose of cefotibiprole medocaril is excreted in the urine. There are no known esterase-deficiency states that would alter the conversion of the prodrug to the active drug. Cefotibiprole medocaril 666.6 mg equates to 500 mg of active cefotibiprole. Like other cephalosporins, cefotibiprole is a six-membered heterocycle joined to a β -lactam ring and contains three variable side chains. Cefotibiprole exerts its action by inhibiting PBPs.¹¹ Cefotibiprole binds tightly to PBP2a (also known as PBP2'), which lends activity against MRSA.^{8,12,13} Cefotibiprole also binds to PBP2x, which is responsible for β -lactam resistance in streptococci.^{13,14} In addition, cefotibiprole binds to PBP2 and PBP3 in *Escherichia coli*; PBP1a-b, PBP2, PBP3, and PBP4 in *Pseudomonas aeruginosa*, and many PBPs in *Enterococcus faecalis*.^{13,15} Similar to ceftazidime,

cefotibiprole does not bind to PBP5/6 in *P. aeruginosa*.^{13,16}

Antimicrobial activity

Methicillin-resistant staphylococci are resistant to most available β -lactam antibiotics due to their production of penicillinase and PBP2a, a low-affinity PBP.⁷ This PBP is connected with methicillin resistance because it functions as a transpeptidase and is not efficiently inhibited by commercially available β -lactam antibiotics. Most β -lactam antibiotics are effective against the other transpeptidases in staphylococci (PBP1, PBP2, and PBP3). Cefotibiprole acylates PBP2a more rapidly than other β -lactam antibiotics and forms a more stable acyl-enzyme complex through a unique interaction with the protein. These properties lead to 100% inhibition of PBP2a and more potent antibacterial activity. Cefotibiprole is a poor substrate for class C β -lactamases and class A enzymes. It is more readily hydrolyzed by class A cephalosporinase from *Proteus vulgaris* 1028 and by extended-spectrum β -lactamases (ESBLs).⁸

Pneumococcal resistance to β -lactam antibiotics is primarily attributable to alterations in PBP1a, PBP2b, and PBP2x. Increases in the minimum inhibitory concentrations (MICs) for β -lactam antibiotics correlate with increases in the amounts of PBP1a, PBP2b, and PBP2x present.^{13,17} In addition, cefotibiprole displayed strong binding to the PBPs essential to *E. coli* (PBP2 and PBP3). Cefotibiprole has exhibited a binding profile similar to that of cefepime and ceftazidime for *P. aeruginosa* but with superior PBP2 binding.¹³

The in vitro potency of cefotibiprole was tested against the most commonly occurring bacterial pathogens collected during a global surveillance study (>60 medical centers in North America, Latin America, and Europe) for 2005–06 (Table 1).¹⁸ A total of 40,675 isolates were tested using broth microdilution

methods. All *S. aureus* strains were inhibited by ≤ 4 $\mu\text{g/mL}$ of cefotibiprole. Cefotibiprole had an MIC₉₀ of ≤ 2 $\mu\text{g/mL}$ against MRSA. Although enterococci are generally not inhibited by cephalosporins, cefotibiprole was highly active against *E. faecalis*, with potency similar to ampicillin, vancomycin, teicoplanin, and linezolid (MIC₉₀ of ≤ 2 $\mu\text{g/mL}$). Cefotibiprole has poor activity against *Enterococcus faecium* (MIC₉₀ of > 8 $\mu\text{g/mL}$). However, for the minority of *E. faecium* that are ampicillin sensitive, cefotibiprole appears to be active.⁸ Cefotibiprole was found to have potency similar to that of imipenem against *Streptococcus pneumoniae* (MIC₉₀ of 0.25 $\mu\text{g/mL}$). Cefotibiprole had an MIC₉₀ of ≤ 0.5 $\mu\text{g/mL}$ against penicillin-resistant *S. pneumoniae*.¹⁸ Against *E. coli*, cefotibiprole had an MIC₉₀ of ≤ 0.12 $\mu\text{g/mL}$, which was at least twofold more potent than cefepime and imipenem. Against *Klebsiella* species, cefotibiprole had an MIC₉₀ of ≤ 8 $\mu\text{g/mL}$, which was more potent than that of ceftriaxone (MIC₉₀ of ≤ 32 $\mu\text{g/mL}$) and cefepime (MIC₉₀ of ≤ 16 $\mu\text{g/mL}$). Potencies for all tested agents, including cefotibiprole, were decreased against *E. coli* and *Klebsiella* species—confirmed ESBL producers—with the exception of the carbapenems (>99% and >98% susceptible, respectively). It is not expected that cefotibiprole will be an effective alternative for ESBL-producing bacteria. Among cephalosporins, cefotibiprole had an MIC₉₀ of ≤ 8 $\mu\text{g/mL}$ against *P. aeruginosa*, which was at least twofold more potent than that of cefepime and ceftazidime. Cefotibiprole was relatively inactive against *Acinetobacter* species (MIC₉₀ of > 8 $\mu\text{g/mL}$) and *Stenotrophomonas maltophilia* (MIC₉₀ of > 8 $\mu\text{g/mL}$). Cefotibiprole has advantages in potency, spectrum of activity (including MRSA and methicillin-resistant coagulase-negative staphylococci [MRCoNS]), and β -lactamase stability when compared with currently marketed extended-spectrum

β -lactams. A large (6680 isolates) surveillance study of gram-positive and gram-negative isolates in Europe reported similar results.¹⁶ Neither surveillance study documented the activity of ceftobiprole against atypical bacteria.

Ceftobiprole was tested against 443 aerobic and anaerobic isolates from pretreatment cultures obtained after debridement from patients with symptomatic, complicated diabetic foot infections (DFIs) at 52 clinical study sites from 2001 through 2004.¹⁹ In this study, ceftobiprole was active against gram-positive anaerobes. Peptostreptococci and clostridia were susceptible (MIC of ≤ 1 $\mu\text{g/mL}$). Among gram-negative anaerobes, *Bacteroides fragilis* and *B. fragilis* group species, many of which were resistant to cefoxitin, and *Prevotella bivia* and *Prevotella melaninogenica* isolates had reduced susceptibility to ceftobiprole.

Antimicrobial resistance

To date, ceftobiprole has demonstrated a low potential to select for resistance.^{8,14,20,21} One investigation found that the highest MIC obtained for *S. aureus* after 50 prolonged subinhibitory serial passages was 8 $\mu\text{g/mL}$, and this was achieved by only 1 of the 10 strains tested.²² The same has been seen for isolates of *Haemophilus influenzae* and *Moraxella catarrhalis*.^{21,23}

Ceftobiprole has decreased binding affinity for several PBPs, including PBP5/6 of *P. aeruginosa*, PBP5 of *E. coli*, and PBP1b and PBP2b of *S. pneumoniae*.^{13,15,16} In addition, as the number of mutations in PBP increased, the MIC values for ceftobiprole also increased.¹⁷

Ceftobiprole is stable in the presence of penicillinases, such as those produced by *S. aureus* as well as the class A and class C β -lactamases produced by some gram-negative bacteria.²⁴ Unfortunately, ceftobiprole appears to be degraded by chromosomal β -lactamases, ESBLs, and carbapenemases.^{9,11,24,25}

Table 1.

Antimicrobial Activity of Ceftobiprole Against Isolates Collected During the SENTRY Antimicrobial Surveillance Program, 2005–06^{18,a}

Organism	No. Isolates Tested	MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)
<i>Staphylococcus aureus</i>	11,784	0.5	2
Methicillin susceptible	6,826	0.25	0.5
Methicillin resistant	4,958	1	2
Coagulase-negative staphylococci	3,283	0.5	2
Methicillin susceptible	784	0.12	0.25
Methicillin resistant	2,499	1	2
<i>Enterococcus faecalis</i>	2,882	0.5	2
<i>Streptococcus pneumoniae</i>	3,632	≤ 0.06	0.25
Penicillin susceptible	2,460	≤ 0.06	≤ 0.06
Penicillin resistant	555	0.25	0.5
β -Hemolytic streptococci	1,565	≤ 0.06	≤ 0.06
<i>Viridans</i> group streptococci	680	≤ 0.06	0.25
<i>Escherichia coli</i>	4,938	≤ 0.06	0.12
ESBL confirmed	318	> 8	> 8
<i>Klebsiella</i> species	2,360	≤ 0.06	> 8
ESBL confirmed	457	> 8	> 8
<i>Enterobacter</i> species	1,373	≤ 0.06	> 8
<i>Citrobacter</i> species	237	≤ 0.06	2
<i>Proteus mirabilis</i>	420	≤ 0.06	0.12
Indole-positive <i>Proteus</i> species	256	≤ 0.06	> 8
<i>Serratia</i> species	557	≤ 0.06	1
<i>Salmonella</i> species	105	≤ 0.06	≤ 0.06
<i>Pseudomonas aeruginosa</i>	2,239	2	> 8
<i>Acinetobacter</i> species	879	> 8	> 8
<i>Haemophilus influenzae</i>	929	≤ 0.06	≤ 0.06
<i>Moraxella catarrhalis</i>	24	≤ 0.06	0.12

^aMIC₅₀ = minimum inhibitory concentration for 50% of isolates, MIC₉₀ = minimum inhibitory concentration for 90% of isolates, ESBL = extended-spectrum β -lactamase.

Ceftobiprole has been shown to be affected by the efflux pump MexXY, which caused increases in MICs.^{26,27} As with other cephalosporins, ceftobiprole may lose activity as the degree of expression of efflux pumps increases by bacteria such as *Pseudomonas* species.

Pharmacokinetics

Protein binding of ceftobiprole is approximately 16% and appears to be independent of ceftobiprole concentration.^{28,29} It is primarily bound to albumin (6.5–11.5%) and α_1 -acid glycoprotein (4.8–6.8%). Changes in the protein binding of ceftobiprole would not change the drug's activity or pharmacokinetic profile.

Ceftobiprole was slowly metabolized in an in vitro human hepatocyte model.¹⁰ Approximately 51% of the drug was metabolized in 24 hours and predominantly converted to an open-ring hydrolysis metabolite. At least three other unidentified metabolites were also produced in trace amounts. Ceftobiprole does not appear to be a substrate or inducer of the cytochrome P-450 (CYP) isoenzyme system. It does minimally inhibit CYP but only at supratherapeutic concentrations. Also, ceftobiprole does not appear to be a substrate or inhibitor of the drug efflux transporter P-glycoprotein.

Ceftobiprole is primarily eliminated as unchanged drug by the kidneys, with up to 89% of the dose

recovered in the urine.¹⁰ In a rat model, ceftobiprole elimination was not affected by the administration of probenecid, indicating that the predominant method of renal elimination is glomerular filtration, not active tubular secretion. Recovery of unchanged drug in the urine in patients with mild to severe renal impairment was 74% and 32%, respectively.³⁰ In a small study of patients with end-stage renal disease receiving intermittent hemodialysis, 28% of a ceftobiprole dose given before hemodialysis was recovered in the dialysate fluid.³¹ Ceftobiprole is effectively removed by dialysis, but further research is needed to support dosing recommendations in this patient population. To date, no studies of patients receiving peritoneal dialysis have been conducted. Ceftobiprole has not been studied in patients with hepatic dysfunction, but ceftobiprole elimination is not expected to be significantly affected, as this is a minor elimination route.

Based on the pharmacokinetic profile of ceftobiprole, the likelihood of significant drug interactions is considered low.¹⁰ To date, clinical drug–drug interaction studies have not been conducted.

When administered as a single dose, ceftobiprole exhibits linear pharmacokinetics at the dose ranges tested.²⁸ The peak concentration is observed at the end of the infusion. Afterward, biphasic elimination occurs, which is consistent with a rapid initial distribution phase followed by a slower terminal elimination phase. The volume of distribution is similar to that of other β -lactam antibiotics, ranging from 17.8 to 19.8 L. Ceftobiprole's half-life is approximately 3 hours. Additional pharmacokinetic parameters are listed in Table 2.

Ceftobiprole 500 or 750 mg infused every 12 hours over 30 minutes produced a very similar pharmacokinetic profile as the profiles observed in single-dose studies (Table 3).²⁹ In addition, drug accumulation appeared to be minimal when day 1 values were compared to those on day 8.

Ceftobiprole 500 mg infused over 2 hours every 8 hours also exhibited similar pharmacokinetics to those seen in the previous multiple-dose studies.³² Accumulation was again minimal, and the half-life was 3 hours. Unlike other studies, the initial volume of distribution was 22 L on day 1 and declined by 29%, to 15.5 L, on day 5.

The effect of infusion duration has been evaluated for ceftobiprole.¹⁰ An infusion of ceftobiprole 750 mg over 30 minutes was compared with ceftobiprole 500 mg infused over 60 minutes. As expected, the mean peak and mean area under the curve were higher for the 750-mg regimen. However, the time above the MIC ($t > \text{MIC}$) for both regimens was approximately 5–6 hours when an MIC of 4 $\mu\text{g/mL}$ was assumed. This supports the ability of ceftobiprole doses to be reduced when coupled with prolongation of the infusion duration.

Ceftobiprole was investigated in patients with no, mild, moderate, or severe renal impairment, defined by creatinine clearance (CL_{cr}) values of >80 , 51–80, 30–50, and <30 mL/min, respectively.³⁰ In this study, a single dose of 250 mg was infused over 30 minutes. As expected, clearance of ceftobiprole decreased as renal function declined. The peak concentration and volume of distribution did not differ significantly among groups. However, the half-life increased as renal function decreased, reaching approximately 11 hours in patients with severe renal impairment. This supports the need to adjust the dos-

Table 2.

Ceftobiprole Pharmacokinetic Parameters After A Single I.V. Infusion of 125, 250, 500, 750, or 1000 mg Over 30 Minutes^{28,a}

Parameter	Ceftobiprole Dose (mg)				
	125	250	500	750	1000
C_{max} ($\mu\text{g/mL}$)	9.87	19.5	35.5	59.6	72.2
$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{hr/mL}$)	20.3	43.7	76.6	135	151
$t_{1/2\alpha}$ (hr)	0.37	0.47	0.57	0.48	0.56
$t_{1/2\beta}$ (hr)	2.84	3.42	3.44	3.47	3.25
Vd_{ss} (L)	17.9	17.8	19.8	18.4	18.9
CL (L/hr)	6.27	5.81	6.54	5.74	6.64
CL_r (L/hr)	4.80	4.35	5.07	4.08	4.16
% urine excretion after 24 hr	74.2	76.1	77.5	71.3	62.5
$t > \text{MIC}$ (%)					
Total	13	29	42	58	58
Unbound	6	17	29	42	42

^a C_{max} = maximum plasma concentration, $\text{AUC}_{0-\infty}$ = area under the plasma concentration–time curve from time zero to infinity, $t_{1/2\alpha}$ = distribution phase half-life, $t_{1/2\beta}$ = terminal elimination half-life, Vd_{ss} = volume of distribution at steady state, CL = total systemic clearance, CL_r = renal clearance, $t > \text{MIC}$ = percentage of time the drug concentration remains above a minimum inhibitory concentration of 4 $\mu\text{g/mL}$ using a 12-hour dosing interval.

ing of ceftobiprole based on renal function. Based on the Canadian prescribing information, no dosage adjustment is required for patients with mild renal impairment (CL_{cr} of 51–80 mL/min).³³ Patients with moderate renal impairment (CL_{cr} of 30–50 mL/min) should receive 500 mg every 12 hours, and patients with severe renal impairment (CL_{cr} of <30 mL/min) should receive 250 mg every 12 hours. There are no current recommendations for patients with end-stage renal disease (CL_{cr} of <10 mL/min) or for those receiving hemodialysis.

Pharmacodynamics

Ceftobiprole exhibits bactericidal activity in vitro. Its pharmacodynamics have been described previously.³⁴ Like other β -lactams, ceftobiprole exhibits concentration-independent killing, and its efficacy can be predicted by the percentage of the dosing interval that the free drug concentration remains above the MIC ($ft > MIC$). The $ft > MIC$ for ceftobiprole differed significantly between gram-positive and gram-negative bacteria. The $ft > MIC$ needed for activity against *S. aureus* is 14.1–27.8%. For gram-negative bacteria (*E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *P. aeruginosa*), the $ft > MIC$ needed for activity ranges from 41.2% to 58.6%. The highest $ft > MIC$ was seen in *P. aeruginosa*. Excluding *P. aeruginosa*, the mean $ft > MIC$ for the remaining gram-negative bacteria tested is 43.1%. Subsequently, pharmacodynamic targets of 30% $ft > MIC$ for documented gram-positive infections and 50% $ft > MIC$ for broad-spectrum coverage against infections with gram-positive and gram-negative bacteria were used to select dosing regimens in Phase III clinical trials.

To date, two Monte Carlo simulations have been performed with ceftobiprole.^{35,36} The first used the initial limited pharmacokinetic data from a single Phase I trial ($n = 12$) in

Table 3.

Ceftobiprole Pharmacokinetic Parameters After Multiple I.V. Infusions of 500 and 750 Mg Over 30 Minutes Every 24 Hours^{29,a}

Parameter	500 mg		750 mg	
	Day 1	Day 8	Day 1	Day 8
C_{max} (μ g/mL)	40.6	44.2	60.7	60.6
$AUC_{0-\infty}$ (μ g·hr/mL)	101	108	156	165
$t_{1/2\alpha}$ (hr)	1.06	1.03	0.96	0.99
$t_{1/2\beta}$ (hr)	3.63	4.04	3.64	4.11
Vd_{ss} (L)	16.4	16.7	16.3	16.1
CL (L/hr)	4.99	5.05	4.85	4.84
% urine excretion after 24 hr	82.2	83.7	87.8	84.4

^a C_{max} = maximum plasma concentration, $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time zero to infinity, $t_{1/2\alpha}$ = distribution phase half-life, $t_{1/2\beta}$ = terminal elimination half-life, Vd_{ss} = volume of distribution at steady state, CL = total systemic clearance.

which subjects received either 500 or 750 mg every 12 hours infused over 30 minutes.³⁵ MIC targets ranging from 0.5 to 16 μ g/mL were selected for the simulation. The results of this simulation are shown in Table 4. Based on the probability of target attainment, ceftobiprole 750 mg every 12 hours would have a high likelihood of therapeutic efficacy.³⁵

The second Monte Carlo simulation used data from Phase I and II trials ($n = 150$).³⁶ Various regimens were simulated, including 500 mg every 8 hours infused over 0.5, 1, and 2 hours and 500 mg every 12 hours infused over 1 hour. The expected distribution of renal function of patients was also included in the simulation. The results of this simulation for patients with normal renal function (CL_{cr} of 120 mL/min) are presented in Table 4. Additional data regarding target achievement for specific pathogens are presented in Table 5. Based on this simulation, a regimen of 500 mg every 12 hours infused over 1 hour was selected for the Phase III trial of ceftobiprole in complicated skin and skin-structure infections (cSSIs) and 500 mg every 8 hours infused over 2 hours was selected for the Phase III trial in nosocomial pneumonia.

Synergy (defined as an increase of 2 $\log_{10}$ colony-forming units/

mL in killing activity at 24 hours with a drug combination compared with a single agent) has been evaluated with ceftobiprole. No synergy was observed when ceftobiprole was combined with tobramycin for MRSA³⁷ or with vancomycin.³⁸ One investigation has described synergy with gentamicin or streptomycin for vancomycin-resistant *E. faecalis*.³⁹ Most drug combinations with ceftobiprole have produced an additive effect for *P. aeruginosa*, and synergy has been seen with levofloxacin or ciprofloxacin, tobramycin, and amikacin in 10%, 27%, and 12% of isolates, respectively.⁴⁰

The postantibiotic effect of ceftobiprole was evaluated in an in vitro study of gram-positive isolates, including *S. aureus* and *E. faecalis*.⁴¹ The postantibiotic effect ranged from 0 to 3.1 hours. The mean postantibiotic effect of ceftobiprole in an in vivo murine lung and thigh model was 4.3 hours for MRSA and 0.5 hour for *S. pneumoniae*.⁴²

Clinical efficacy

To date, the results of two Phase III clinical trials investigating ceftobiprole for the treatment of cSSIs have been published.^{43,44} Phase III clinical trials of ceftobiprole for the treatment of hospital-acquired pneumonia and community-acquired pneumonia

Table 4.
Probability of Target Attainment Using Various Ceftobiprole Regimens^a

Infusion Regimen and MIC	Probability of Achieving <i>ft</i> > MIC, % ^b	
	30%	50%
500 mg q 8 hr over 30 min ³⁵		
2 µg/mL	...	100
4 µg/mL	100	99
500 mg q 8 hr over 30 min ³⁶		
2 µg/mL	97	88
4 µg/mL	88	71
500 mg q 8 hr over 1 hr ³⁶		
2 µg/mL	98	90
4 µg/mL	91	74
500 mg q 8 hr over 2 hr ³⁶		
2 µg/mL	99	94
4 µg/mL	96	80
500 mg q 12 hr over 1 hr ³⁶		
2 µg/mL	92	74
4 µg/mL	74	47
500 mg q 12 hr over 30 min ³⁵		
2 µg/mL	...	100
4 µg/mL	100	1
750 mg q 12 hr over 30 min ³⁵		
2 µg/mL	...	100
4 µg/mL	100	78

^aMIC = minimum inhibitory concentration, *ft* > MIC = percentage of the dosing interval that the drug concentration remains above the MIC.

^bPharmacodynamic targets of 30% *ft* > MIC for gram-positive infections and 50% *ft* > MIC for broad-spectrum coverage against both gram-positive and gram-negative infections were used to select dosing regimens in Phase III clinical trials.

^cData not available.

Table 5.
Probability of Target Attainment for Ceftobiprole in Various Pathogens^{36,a}

Infusion Regimen and Pathogen	Probability of Achieving <i>ft</i> > MIC, %	
	30%	50%
500 mg q 12 hr over 1 hr		
Methicillin-resistant <i>Staphylococcus aureus</i> (<i>n</i> = 170)	98.4	92.6
Methicillin-susceptible <i>S. aureus</i> (<i>n</i> = 291)	99.5	96.9
500 mg q 8 hr over 2 hr		
Methicillin-resistant <i>S. aureus</i> (<i>n</i> = 170)	99.9	98.8
Methicillin-susceptible <i>S. aureus</i> (<i>n</i> = 291)	99.9	98.8
AmpC-producing gram-negative bacilli (<i>n</i> = 166)	...	88.9
Non-AmpC-producing gram-negative bacilli (<i>n</i> = 206)	...	94.8
<i>Pseudomonas aeruginosa</i> (<i>n</i> = 407)	...	66.4

^a*ft* > MIC = percentage of the dosing interval that the drug concentration remains above the minimum inhibitory concentration.

^bData not available.

(CAP) have been completed. A Phase III clinical trial of ceftobiprole for use in patients with fever and neutropenia after chemotherapy for cancer has been suspended due to administrative reasons that are unrelated to safety,⁴⁵ and a Phase II clinical trial involving *S. aureus* bacteremia was withdrawn before study recruitment due to a lack of an appropriate patient population.⁴⁶

cSSSIs. A multicenter, global, randomized, double-blind trial was conducted to compare ceftobiprole with vancomycin in the treatment of cSSSIs caused by gram-positive bacteria.⁴³ Patients were randomized to receive either i.v. ceftobiprole 500 mg every 12 hours infused over 1 hour or vancomycin 1 g every 12 hours for 7–14 days. The primary objective was to assess noninferiority on the basis of the clinical cure rates after the completion of therapy. Patients were eligible for the trial if they were age 18 years or older and were diagnosed with a cSSI caused by a documented or suspected gram-positive bacteria. Patients were excluded if they had a history of an allergic reaction with or an intolerance to either cephalosporins or vancomycin, severe renal dysfunction (CL_{cr} of <30 mL/min), hepatic dysfunction, or a condition that might affect adherence to the protocol requirements. The following subgroups were also excluded: pregnant or lactating women; neutropenic patients; patients infected with human immunodeficiency virus with CD4 T-lymphocyte counts of $<0.2 \times 10^9/L$; patients with DFIs, osteomyelitis, or infections associated with bites; and patients who had received antibiotic therapy for more than 24 hours in the 7 days before enrollment.

Patients were enrolled into one of the protocol-defined disease strata (wound infection, abscess, cellulitis) and randomly assigned in a 1:1 ratio to receive either ceftobiprole or vancomycin. At the investigator's discretion, empirical therapy with

aztreonam or metronidazole was permitted for the first 48 hours of treatment. Vancomycin concentrations were monitored and adjusted according to the individual investigator's practices.

Patients were evaluated before the start of therapy (baseline) and during therapy on days 4, 8, and 14. An end-of-therapy (EOT) visit was performed within 24 hours after the last administration of the study drug, and a test-of-cure (TOC) visit was performed 7–14 days after the EOT visit. Patients considered clinically cured at the TOC visit were evaluated for relapse at a late follow-up visit 28–35 days after the EOT visit. Noninferiority was defined as a lower 95% confidence interval (CI) limit of $\geq -10\%$.

A total of 784 patients were enrolled. Demographics and baseline characteristics were comparable between groups, and the duration of treatment was the same in both groups. The clinical cure rates were similar in both groups at the TOC visit (77.8% in the ceftobiprole group versus 77.5% in the vancomycin group; 95% CI, -5.5% to 6.1%). The microbiological outcome of eradication or presumed eradication at the TOC visit in microbiologically evaluable patients was 94.2% in the ceftobiprole group and 93.5% in the vancomycin group (95% CI, -3.8% to 5.2%).

The overall clinical cure rate for cSSSIs caused by *S. aureus* was 94.6% in the ceftobiprole group and 94.2% in the vancomycin group (95% CI, -4.3% to 5.2%). When considering only cSSSIs caused by MRSA, the clinical cure rate was 91.8% in the ceftobiprole group and 90% in the vancomycin group (95% CI, -8.4% to 12.1%). There were no significant differences in the overall rates of adverse effects between groups.

The second Phase III clinical trial was a randomized, double-blind, global, multicenter trial that compared ceftobiprole to vancomycin plus ceftazidime for the treatment

of cSSSIs caused by gram-positive or gram-negative bacteria.⁴⁴ Patients were randomized to receive either i.v. ceftobiprole 500 mg every 8 hours infused over 2 hours or vancomycin 1 g every 12 hours infused over 1 hour plus ceftazidime 1 g every 8 hours infused over 2 hours. The primary objective was to assess noninferiority on the basis of the clinical cure rates after the completion of therapy. Patients were eligible for the trial if they were age 18 years or older and were diagnosed with a cSSSI. Patients were excluded if they had a foreign body infection, osteomyelitis, critical limb ischemia, or septic arthritis.

Patients were randomly assigned in a 2:1 ratio to either the ceftobiprole group or comparator group (vancomycin plus ceftazidime) for 7–14 days. At the investigator's discretion, empirical therapy with metronidazole was permitted for the first 48 hours of treatment. Vancomycin concentrations were monitored and adjusted according to the individual investigator's practices. Clinical and microbiological outcomes were assessed at a TOC visit 7–14 days after the completion of therapy. Noninferiority was defined as a lower 95% CI limit of $\geq -10\%$ for the difference in the clinical cure rate.

A total of 828 patients were enrolled. Demographics and baseline characteristics were comparable between the groups, and there was no difference in the duration of treatment between groups. At the TOC visit, the cure rates were similar in both groups (81.9% in the ceftobiprole group versus 80.8% in the comparator group; 95% CI, -4.5% to 6.7%). The clinical cure rate at the TOC visit in the clinically evaluable population was 90.5% in the ceftobiprole group and 90.2% in the comparator group (95% CI, -4.2% to 4.9%). The microbiological eradication rate at the TOC visit was 88% in the ceftobiprole group and 89% in the comparator group (95% CI, -6.4% to 4.5%).

The overall clinical cure rate for cSSSIs caused by *S. aureus* was 92.3% in the ceftobiprole group and 91.4% in the comparator group (95% CI, -5.0% to 7.7%). When considering only cSSSIs caused by MRSA, the clinical cure rate was 89.7% in the ceftobiprole group and 86.1% in the comparator group (95% CI, -8.0% to 19.7%). The rate of adverse effects did not significantly differ between the groups.

Endocarditis and orthopedic infections. A study was conducted to test the susceptibility of ceftobiprole against methicillin-resistant staphylococcal isolates associated with endocarditis and bone and joint infections.⁴⁷ The study included 37 MRSA and 51 MRCoNS isolates recovered from patients with endocarditis from 1985 through 2005 and 31 MRSA and 65 MRCoNS isolates recovered from patients with bone and joint infections from 1999 through 2005. In addition to ceftobiprole, the isolates were tested against daptomycin, linezolid, and vancomycin. Both the MIC and minimum bactericidal concentration (MBC) values for ceftobiprole were $\leq 2 \mu\text{g/mL}$, with the exception of 1 orthopedic MRCoNS isolate. Ceftobiprole and daptomycin were bactericidal (MBC:MIC ratio of <32) against all isolates. The study showed ceftobiprole to have an MBC of $2 \mu\text{g/mL}$ for 90% of in vitro MRSA and MRCoNS isolates associated with endocarditis and bone and joint infections.

In a study comparing the efficacy of ceftobiprole to that of vancomycin against MRSA and vancomycin-intermediate *S. aureus* (VISA) in a rabbit model of aortic valve endocarditis, ceftobiprole and vancomycin produced similar reductions in tissue burdens for MRSA infections, and ceftobiprole was found to be superior to vancomycin for the treatment of endocarditis caused by VISA.⁴⁸

Pneumonia. In a study conducted to compare the in vivo activity of ceftobiprole with that of ceftriaxone

in a mouse model of acute pneumococcal pneumonia, there was no significant difference in cumulative survival rates between the two antibiotics, but 100% survival was obtained at a fivefold lower total daily ceftobiprole dose than the dose of ceftriaxone used.²¹

A double-blind, multicenter, non-inferiority trial was conducted to compare the efficacy of ceftobiprole to that of ceftazidime plus linezolid in patients with nosocomial pneumonia.⁴⁹ Patients were randomized to receive either i.v. ceftobiprole 500 mg every 8 hours infused over 2 hours or ceftazidime 2 g every 8 hours infused over 2 hours plus linezolid 600 mg every 12 hours infused over 1 hour for 7–14 days. The primary objective was to demonstrate the noninferiority of ceftobiprole compared to ceftazidime plus linezolid with respect to the clinical cure rate at the TOC visit in subjects in both the clinically evaluable and intent-to-treat populations. Noninferiority was defined as a lower 95% CI limit of $\geq -15\%$. Patients were eligible for the trial if they were age 18 years or older and were diagnosed with nosocomial pneumonia or ventilator-associated pneumonia (VAP) as defined per the study protocol.

A total of 781 patients were enrolled. Demographics and baseline characteristics were comparable between the groups. The cure rate at the TOC visit in the intent-to-treat population was 49.9% in the ceftobiprole group and 52.8% in the comparator group (95% CI, -10.0% to 4.1%). Among patients without VAP in the intent-to-treat population, the cure rate was 59.2% in the ceftobiprole group and 58.9% in the comparator group (95% CI, -7.8% to 8.3%). Among patients with VAP in the intent-to-treat population, the cure rate was 23.5% in the ceftobiprole group and 36.2% in the comparator group (95% CI, -25.0% to -0.3%).

The clinical cure rate at the TOC visit in the clinically evaluable popu-

lation was 69.3% in the ceftobiprole group and 71.6% in the comparator group (95% CI, -10.3% to 5.7%). Among patients without VAP in the clinically evaluable population, the cure rate was 77.4% in the ceftobiprole group and 76.3% in the comparator group (95% CI, -7.3% to 9.5%). Among patients with VAP in the clinically evaluable population, the cure rate was 38.5% in the ceftobiprole group and 56.7% in the comparator group (95% CI, -36.4% to 0%). Overall, the mortality rate was 23% in the ceftobiprole group and 22% in the comparator group (95% CI, -5.1% to 6.6%).

A randomized, double-blind trial was conducted to compare the efficacy of ceftobiprole to that of ceftriaxone with or without linezolid in patients hospitalized with CAP.⁵⁰ Patients were randomized to receive either i.v. ceftobiprole 500 mg every 8 hours infused over 2 hours with or without placebo every 12 hours infused over 1 hour or ceftriaxone 2 g daily infused over 30 minutes with or without linezolid 600 mg every 12 hours infused over 1 hour. The primary objective was to demonstrate the noninferiority of ceftobiprole compared to ceftriaxone with or without linezolid with respect to the clinical cure rate at the TOC visit in patients hospitalized with CAP. Noninferiority was defined as a lower 95% CI limit of $\geq -10\%$. Patients were eligible for the trial if they were age 18 years or older and met the clinical and radiological criteria for acute bacterial CAP requiring treatment with i.v. antibiotics for 72 hours or longer.

A total of 666 patients were randomized and enrolled. The ceftobiprole group had more polymicrobial infections at baseline than did the comparator group (20% versus 8%, $p = 0.016$). All other demographics and baseline characteristics were comparable between the groups. The cure rate at the TOC visit in the intent-to-treat population was 77.4%

in the ceftobiprole group and 80.2% in the comparator group (95% CI, -8.9% to 3.5%). The clinical cure rate at the TOC visit in the clinically evaluable population was 86.7% in the ceftobiprole group and 87.6% in the comparator group (95% CI, -6.9% to 5.2%).

Adverse effects

The adverse effects experienced by patients receiving ceftobiprole versus a comparator treatment varied little.^{43,44,50} Overall, approximately 50% of patients experienced at least one adverse effect. The most common adverse effects were gastrointestinal upset and headaches, and these varied from mild to moderate in severity.

In the trial comparing ceftobiprole to vancomycin, the most frequent adverse effects associated with ceftobiprole were nausea (14%), dysgeusia (8%), vomiting (7%), and headache (7%)⁴³. Gastrointestinal upset was the primary reason for discontinuation of both ceftobiprole and vancomycin therapy (25% and 17%, respectively). Of the 771 total patients, 47 reported at least one serious adverse event (6% with ceftobiprole and 6% with vancomycin). In the vancomycin group, three deaths occurred but were deemed unrelated to the study drug. In another randomized, double-blind trial that compared ceftobiprole with vancomycin plus ceftazidime, results were similar to the aforementioned trial.⁴⁴ The most common adverse effects in the ceftobiprole group were nausea (11%), infusion-site reaction (9%), diarrhea (8%), headache (8%), and vomiting (6%). In patients treated with vancomycin and ceftazidime, adverse effects included hypersensitivity (10%), infusion-site reaction (9%), diarrhea (6%), insomnia (5%), headache (5%), and constipation (5%). Discontinuation of ceftobiprole or the comparator treatment due to adverse effects equated to 5% and 6% of patients, respectively.

One study found that the most common patient complaint was “caramel-like taste disturbances” (dysgeusia) when the medication was administered at higher doses. This was found to be most likely a result of the metabolism of ceftobiprole medocaryl to diacetyl.^{28,29}

Dosage and administration

Ceftobiprole has not received the Food and Drug Administration (FDA)-approved labeling. The two published Phase III trials for treatment of cSSSIs used ceftobiprole 500 mg every 12 hours infused over 1 hour and 500 mg every 8 hours infused over 2 hours. Ceftobiprole was noninferior and had an equivalent safety profile to the comparator treatment in both trials.^{43,44} Phase III trials for CAP and nosocomial pneumonia used 500 mg every 8 hours infused over 2 hours.^{49,50}

Ceftobiprole has been approved for use in Canada. According to the Canadian prescribing information, the recommended dosage is 500 mg every 12 hours infused over 1 hour for the treatment of cSSSIs caused by gram-positive pathogens.³³ The approved regimen for infections caused by susceptible gram-negative pathogens, polymicrobial infections, and DFIs is 500 mg every 8 hours infused over 2 hours.

Dosage adjustments for renal impairment are also required. Based on the Canadian prescribing information, dosage adjustments are 500 mg every 12 hours infused over 2 hours for moderate renal impairment and 250 mg every 12 hours infused over 2 hours for severe renal impairment.³³ There currently is no recommendations for patients with end-stage renal disease or receiving dialysis.

Ceftobiprole is compatible with 0.9% sodium chloride injection, 5% dextrose injection, and lactated Ringer's solution.³³ Compatibility with other medications has not been established. After reconstitution with sterile water for injection or 5% dex-

trose injection, ceftobiprole is stable for 1 hour at 25 °C and 24 hours at 2–8 °C.³³ Reconstituted solution should be protected from light. When mixed for infusion, stored at 25 °C, and protected from light, ceftobiprole is stable for 24 hours with both 0.9% sodium chloride injection and lactated Ringer's solution and 8 hours with 5% dextrose injection. If not protected from light, ceftobiprole is stable for 12 hours with both 0.9% sodium chloride injection and lactated Ringer's solution and 8 hours with 5% dextrose injection. If the infusion solution is stored at 2–8 °C and protected from light, it is stable for 96 hours with both 0.9% sodium chloride injection and 5% dextrose injection. Infusion solutions made with lactated Ringer's solution should not be refrigerated. Total stability time of the infusion solution includes the total time from reconstitution to completion of the infusion.

Place in therapy

Ceftobiprole has the potential to be used as monotherapy for the treatment of pneumonia and cSSSIs. Patients with DFIs and osteomyelitis were excluded from the cSSSI clinical trials, and ceftobiprole may not be optimal therapy for these infections. In addition, patients with renal dysfunction were excluded from clinical trials.

Ceftobiprole covers gram-positive organisms and has in vitro activity against both MRSA and penicillin-resistant *S. pneumoniae*. In addition, it exhibits the activity of extended-spectrum cephalosporins against gram-negative organisms. Among cephalosporins, ceftobiprole has potency against *P. aeruginosa* similar to that of cefepime and ceftazidime. Ceftobiprole has anaerobic coverage. It is relatively inactive against *Acinetobacter* species and *S. maltophilia*. There is no documented activity against atypical bacteria. Ceftobiprole remains under review by FDA.

Conclusion

Ceftobiprole is a novel, broad-spectrum, parenteral cephalosporin undergoing Phase III clinical trials. Its broad spectrum of activity makes it a candidate for monotherapy, either empirically or for treatment, of cSSSIs and pneumonias that have required combination therapy in the past.

After this manuscript was accepted for publication, Johnson & Johnson Pharmaceutical Research & Development received a complete response letter for ceftobiprole from FDA regarding a new drug application for the use of ceftobiprole for the treatment of cSSSIs. FDA determined that data from studies BAP00154 and BAP00414 cannot be relied on; inspections and audits of approximately one third of the clinical trial sites found the data from a large proportion of these sites to be unreliable or unverifiable.^{51,52} These findings raised concerns regarding the overall integrity of the data. FDA has requested additional information and recommended that additional clinical studies be conducted before approval of ceftobiprole for the treatment of cSSSIs can be considered.

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