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ADIS DRUG CLINICAL Q&A

Ceftobiprole medocaril: a guide to its use in hospital- or community-acquired pneumonia in the EU

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Abstract Ceftobiprole medocaril (Zevtera®, Mabelio®), the prodrug of ceftobiprole, is a fifth generation, parenteral cephalosporin that was recently approved for the treatment of hospital-acquired pneumonia (HAP, with the exclusion of ventilator-associated pneumonia) and community-acquired pneumonia (CAP) in the EU. It displays broad-spectrum activity against Gram-positive and Gram-negative pathogens that cause HAP and CAP, including meticillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. In pivotal trials, ceftobiprole medocaril showed noninferior clinical efficacy relative to ceftazidime + linezolid in patients with HAP, and ceftriaxone ± linezolid in patients with CAP, and was generally well tolerated.

Adis evaluation of intravenous ceftobiprole medocaril in the treatment of hospital- and community-acquired pneumonia
What are its key clinical benefits?
Provides broad-spectrum activity against Gram-positive bacteria (including meticillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*) and Gram-negative bacteria
Shows low potential for the selection of resistance among clinically relevant pathogens in in vitro resistance development studies
Effective in the treatment of patients with HAP (excluding those with VAP) and CAP (including those at risk for poor outcomes)
May be used at reduced doses in patients with severe renal impairment (with caution) or end-stage renal disease
Provides a simple monotherapy option for initial empirical treatment
What are its key clinical limitations?
Not approved to treat VAP (clinical efficacy was not noninferior vs. a comparator) or patients aged <18 years (lack of data)
Requires intravenous administration over a period of 2 h every 8 h

CAP community-acquired pneumonia, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia

What is the rationale for developing ceftobiprole medocaril?

Hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP) are often caused by multidrug-resistant (MDR) bacterial pathogens, which are associated with poor treatment outcomes and higher treatment costs [1, 2]. The selection of antibacterial treatment for these infections should be based on the onset of HAP (i.e. early or late) [3], severity of CAP [4] and risk factors for specific pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), highly drug resistant *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. [3, 4].

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The initial empirical therapy for HAP and CAP includes a combination of a broad-spectrum antibacterial agent and specific agent(s) targeted at problematic pathogens [3, 4]. Second- or third-generation cephalosporins, either alone or in combination with another agent, are options for the initial empirical treatment of HAP and CAP [3, 4]. If MRSA is suspected or identified, the use of vancomycin, linezolid or teicoplanin ± rifampin is recommended [3, 4]. However, these MRSA agents have tolerability limitations, such as vancomycin-related nephrotoxicity [5], and linezolid-associated myelosuppression [6].

A single well-tolerated agent with broad-spectrum antibacterial activity, including activity against MDR pathogens, may simplify the initial empirical therapy for HAP and CAP. Ceftobiprole medocaril (Zevtera®, Mabelio®) is a parenteral, fifth generation, broad-spectrum cephalosporin with anti-MRSA activity [7]. It is the first anti-MRSA cephalosporin to receive approval in the EU for the treatment of both HAP [excluding ventilator-associated pneumonia (VAP)] and CAP [8].

How does ceftobiprole work?

As with other β-lactam antibacterial agents, ceftobiprole (the active metabolite of the prodrug ceftobiprole medocaril) exerts its antibacterial action by binding to penicillin-binding proteins (PBPs) and irreversibly inhibiting their transpeptidase activity [7], which is essential for the synthesis of the peptidoglycan layer of bacterial cell walls. The anti-MRSA activity of ceftobiprole is attributed to its tight binding to PBP2a (encoded by the *mec*A gene) that confers meticillin resistance in *S. aureus* [7]. Ceftobiprole showed in vitro activity against MRSA strains that express divergent *mecA* gene homologues (*mecC* or *mecA*LGA251) [8]. Ceftobiprole also demonstrated high binding affinity for multiple PBPs in *S. pneumoniae* (including PBP-1a and -2x, which are involved in conferring penicillin resistance), *Escherichia coli* (including PBP-2 and -3), *P. aeruginosa* (including PBP2) and enterococci (PBP5, which confers penicillin resistance) [9, 10].

What is its antibacterial activity against specific pathogens?

As reviewed previously [11], ceftobiprole showed good in vitro activity against a broad spectrum of Gram-positive and Gram-negative pathogens that cause HAP and CAP; data for some clinically relevant pathogens are summarized in Table 1. Among Gram-positive bacteria, ceftobiprole also showed potent activity against vancomycin-intermediate *S. aureus* (VISA), heterogeneous VISA, vancomycin-resistant *S. aureus*, *S. aureus* strains that were not susceptible to linezolid, meticillin-resistant and meticillin-susceptible coagulase-negative staphylococci, β-haemolytic streptococci, viridans group streptococci and *Enterococcus faecalis*. Among Gram-negative bacteria, ceftobiprole showed in vitro activity against *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* strains that do not produce extended spectrum β-lactamase (ESBL),

Table 1 In vitro activity of ceftobiprole against typical bacteria causing hospital- or community-acquired pneumonia (reviewed by Syed [11])

Species (no. of isolates[a])	MIC_{90} (mg/L)	Susceptible isolates (%)[b]
Gram-positive bacteria		
Staphylococcus aureus (26,931)	1–2	99.5–99.9
MRSA (9386)	2	98.3–99.6
Streptococcus pneumoniae (8581)	0.25–0.5	99.3–100
PRSP (916)	0.5–2	100
Gram-negative bacteria		
Haemophilus influenzae (3389)	≤0.06–0.25	
Moraxella catarrhalis (519)	0.12–0.5	
Enterobacteriaceae (21,817)	>8–32	74.7–83.4
Escherichia coli (16,785)	0.12–>8	
Pseudomonas aeruginosa (>7106)	>8 to >16	64.6[c]
Klebsiella spp. (4618)	0.125 to >8	61.6
Acinetobacter spp. (1489)	>8 to >32	

MIC_{90} minimum inhibitory concentration required to inhibit 90 % of isolates, *MRSA* meticillin-resistant *S. aureus*, *PRSP* penicillin-resistant *S. pneumoniae*

[a] Collected from Europe between 2005–2011, including data from the SENTRY antimicrobial surveillance programme and the CLASS study

[b] Based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints at the time of studies. Current breakpoints are available at http://www.eucast.org/

[c] Based on a non-species specific breakpoint

Table 2 Prescribing summary of ceftobiprole medocaril (Zevtera®, Mabelio®) in the treatment of adults aged ≥18 years with hospital- or community-acquired pneumonia in the EU. Consult local prescribing information for further details

How is it available and what is its stability?	
Availability	Vial containing 500 mg of ceftobiprole powder equivalent to 666.6 mg of ceftobiprole medocaril sodium
	After reconstitution, 1 mL of solution contains 50 mg of ceftobiprole
Stability after reconstitution	Use the solution immediately once reconstituted
	Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 1 h at 25 °C and up to 24 h at 2–8 °C
What is its administration regimen?	
Hospital-acquired pneumonia (excluding ventilator-associated pneumonia)	500 mg administered every 8 h as a 2-h intravenous infusion
Community-acquired pneumonia	500 mg administered every 8 h as a 2-h intravenous infusion
	After completing ≥3 days of treatment, consider switching to an appropriate oral antibiotic depending upon the patient's clinical response
What are the contraindications to its use?	
Hypersensitivity to the drug or any of its excipients or cephalosporin antibacterials	
Immediate and severe hypersensitivity to any other type of β-lactam antibacterial agent (e.g. penicillins or carbapenems)	
How should it be used in patients with renal impairment or supra-normal renal function?	
CL_{CR} >150 mL/min	Increase infusion duration to 4 h
CL_{CR} 50–80 mL/min	No dosage adjustment required
CL_{CR} 30 to <50 mL/min	500 mg every 12 h infused over 2 h
CL_{CR} <30 mL/min	250 mg every 12 h infused over 2 h (use with caution; data are limited)
ESRD ± intermittent dialysis	250 mg every 24 h
How should it be used in other special patient populations?	
Elderly patients with normal renal function	No dosage adjustments are necessary
Patients with hepatic impairment	No dosage adjustments are necessary
Patients who are obese	No dosage adjustments are necessary
Women who are pregnant	Do not use unless strictly necessary (lack of data)
Women who are breastfeeding	Discontinue breastfeeding or discontinue/abstain from ceftobiprole medocaril therapy
What are some of the other special warnings/precautions pertaining to its use?	
Use with caution in patients with a history of non-severe hypersensitivity to other β-lactam antibacterials	
May cause seizures (most commonly in patients with pre-existing CNS or seizure disorders), super-infection (in patients with nonsusceptible pathogens) or *Clostridium difficile*-associated diarrhoea	
What is its pharmacokinetic profile?	
Time to steady state	1 day
Plasma half-life	≈3 h
Metabolism	Rapidly converted by non-specific plasma esterases to the active metabolite ceftobiprole, which undergoes minimal metabolism
Elimination	Primarily as unchanged ceftobiprole in the urine (via glomerular filtration)
What potential drug interactions are associated with its use?	
Drugs eliminated by OATP1B1 and OATP1B3 (e.g. statins, glyburide and bosentan)	Concentrations of these drugs may increase (ceftobiprole inhibits these hepatocyte uptake transporters)
Cytochrome P450 interactions	Potential for such interactions cannot be ruled out (concentrations of ceftobiprole used in in vitro studies were limited by solubility)
Drugs with a narrow therapeutic index	Use with caution (clinical interaction studies have not been performed)

CL_{CR} creatinine clearance, *ESRD* end-stage renal disease, *OAT* organic anion transporter

but is generally inactive against ESBL-producing strains of these organisms [11].

In infection models, ceftobiprole showed bactericidal effects against *S. aureus* (including MRSA), *S. pneumoniae* (including MDR strains), *E. coli, P. aeruginosa*, *K. pneumoniae*, *E. cloacae* and *H. influenzae* [11]. In in vitro resistance selection studies, ceftobiprole showed low potential for resistance evolution in Gram-negative and

drug-resistant Gram-positive (including MRSA) respiratory pathogens [11].

For whom is ceftobiprole medocaril indicated?

Ceftobiprole medocaril is approved in 12 countries in the EU and in Switzerland for the treatment of adults with HAP (excluding VAP) and CAP [8]. Table 2 presents a summary of the prescribing information for ceftobiprole medocaril in the EU [8]. Official guidance on the appropriate use of antibacterial agents should be considered when using ceftobiprole medocaril.

What is the efficacy of ceftobiprole medocaril in hospital-acquired pneumonia?

Ceftobiprole medocaril was noninferior to ceftazidime + linezolid in terms of clinical cure rates at the test-of-cure (TOC) visit in adult patients with HAP (non-VAP or VAP) in a double-blind trial (Table 3) [12]. In subgroup analyses, the noninferiority of ceftobiprole medocaril was demonstrated in the predefined subgroup of patients with non-VAP ($n = 571$), but not in those with VAP ($n = 210$). In patients with non-VAP, the clinical cure rate in the intent-to-treat (ITT) population was 59.6 % with ceftobiprole medocaril versus 58.8 % with ceftazidime + linezolid [between-group difference (BGD) +0.8; 95 % CI −7.3 to 8.8]; the corresponding rate in the clinically evaluable (CE) population was 77.8 versus 76.2 % (BGD +1.6; 95 % CI −6.9 to 10.0). However, in patients with VAP, the clinical cure rates with ceftobiprole medocaril versus ceftazidime + linezolid were 23.1 versus 36.8 % (BGD −13.7; 95 % CI −26.0 to −1.5) in the ITT population and 37.7 versus 55.9 % (BGD −18.2; 95 % CI −36.4 to 0) in the CE population. The differential outcome between non-VAP and VAP subgroups was thought to be related to the small sample size and the substantial heterogeneity in baseline characteristics in the VAP subgroup [12].

Clinical cure rates for the most commonly isolated baseline pathogens in patients with non-VAP are shown in

Table 3 Efficacy of intravenous ceftobiprole medocaril at the test-of-cure visit (7–14 days post-treatment) in adults with hospital- or community-acquired pneumonia participating in double-blind multinational phase 3 trials

Treatment regimen (administered intravenously for 7–14 days)	Clinical cure (% pts) [no. of pts]		Microbiological eradication (% pts) [no. of pts]	
	ITT[a]	CE[b]	Microbiological ITT[c]	ME[d]
In pts with HAP (non-VAP or VAP) [12]				
Ceftobiprole medocaril 500 mg every 8 h	49.9 [391]	69.3 [251]	39.0 [269]	53.7 [162]
Ceftazidime 2 g every 8 h + linezolid 600 mg every 12 h	52.8 [390]	71.3 [244]	47.6 [267]	62.4 [170]
Between-group difference (95 % CI)	−2.9 (−10.0 to 4.1)[e]	−2.0 (−10.0 to 6.1)[e]	−8.5 (−16.9 to −0.2)	−8.6 (−19.2 to 1.9)
In pts with CAP [8, 13]				
Ceftobiprole medocaril 500 mg every 8 h	76.4 [314]	86.6 [231]	80.5 [87]	88.2 [68]
Ceftriaxone 2 g once daily ± linezolid 600 mg every 12 h	79.3 [324]	87.4 [238]	81.4 [97]	90.8 [76]
Between-group difference (95 % CI)	−2.9 (−9.3 to 3.6)[e]	−0.8 (−6.9 to 5.3)[e]	−1.0 (−12.4 to 10.4)	−2.6 (−12.6 to 7.5)

CAP community-acquired pneumonia, *CE* clinically evaluable, *HAP* hospital-acquired pneumonia, *ITT* intent-to-treat, *ME* microbiologically evaluable, *pts* patients, *TOC* test-of-cure, *VAP* ventilator-associated pneumonia

[a] All randomized pts

[b] HAP: all treated pts excluding those who had a missing TOC visit, received an effective non-study antibiotic, received only a short course of study drugs, had pathogen(s) resistant to either study regimen, had an early or unrelated death, did not have a confirmed HAP, or had other protocol violations. CAP: all treated pts excluding those who received only a short course of study drugs (for <48 h, <80 % of the intended doses or cured with <5 days of therapy), received a non-study antibiotic with activity against CAP pathogens, had pathogen(s) resistant to either study regimen, did not have a pulmonary infiltrate confirmed by central radiology, had a positive baseline immunoglobulin M serology for *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*, with no typical bacterial CAP co-pathogen identified, missed a TOC visit or died prior to TOC from a cause unrelated to pneumonia

[c] All ITT pts with a typical bacterial pneumonia pathogen isolated at baseline

[d] All microbiological ITT pts with HAP who were also clinically evaluable, excluding those who were not evaluable at TOC for a microbiological outcome (eradication, presumed eradication, colonization, persistence, presumed persistence, super infection or not evaluable) or all CE pts with CAP with a typical bacterial pneumonia pathogen isolated at baseline

[e] Primary endpoint (ceftobiprole medocaril was noninferior to the comparator)

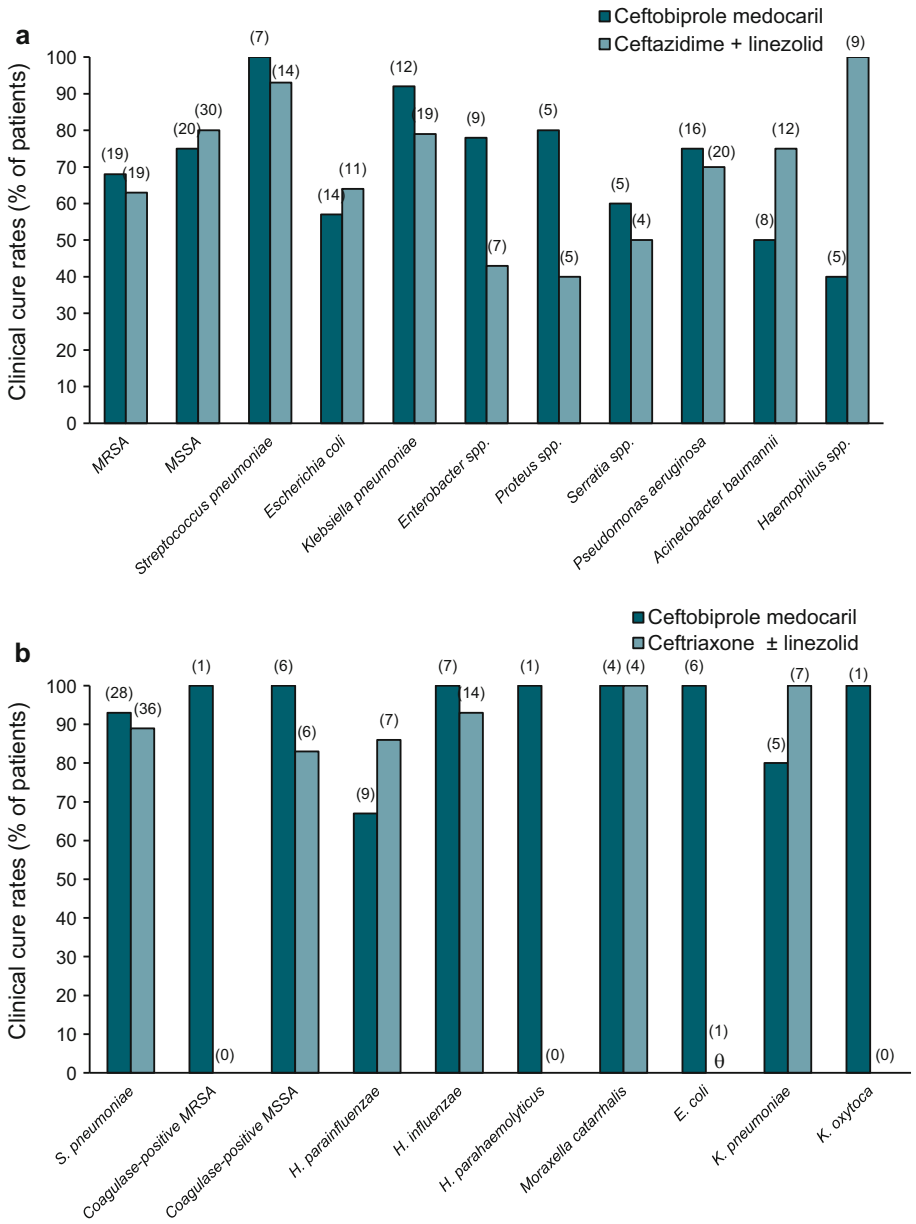

Fig. 1 Clinical cure rates at the test-of-cure visit by the most common baseline pathogens in the microbiologically evaluable population of patients with **a** hospital-acquired pneumonia (excluding ventilator-associated pneumonia) [12] **b** community-acquired pneumonia [13] in pivotal clinical trials. The bracketed *numbers* above the *bars* are the numbers of patients with that particular baseline pathogen. θ indicates 0 % clinical cure rate. *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *S. aureus*

Fig. 1a [12]. The rates were generally similar for Gram-positive and most Gram-negative pathogens. In the CE population of patients with non-VAP, clinical cure rates with ceftobiprole medocaril were generally similar to those with ceftazidime + linezolid in subgroup analyses by baseline demographic and clinical characteristics (age, sex, geographical region, Acute Physiology and Chronic Health Evaluation II score, care facility [intensive care unit (ICU) vs. non-ICU], and use of pre-study antibiotics and antipseudomonal antibiotics) [12].

Microbiological eradication rates in patients with HAP (non-VAP or VAP) are summarized in Table 3 [12]. In patients with non-VAP, the rates at the TOC assessment in the ceftobiprole medocaril versus ceftazidime + linezolid groups were 48.6 versus 53.6 % (BGD −5.0; 95 % CI −15.3 to 5.3) in the microbiological ITT population and 62.9 versus 67.5 % (BGD −4.6; 95 % CI −16.7 to 7.6) in the microbiologically evaluable (ME) population. The corresponding rates in patients with VAP were 20.0 versus 34.9 % (BGD −14.9; 95 % CI −27.9 to −1.9) and 30.4 versus 50.0 % (BGD −19.6; 95 % CI −38.8 to −0.4), respectively [12].

In the ITT population, 30-day all-cause mortality rates in the ceftobiprole medocaril versus ceftazidime + linezolid groups in patients with HAP (non-VAP or VAP), non-VAP and VAP were 19.4 versus 18.5 %, 16.7 versus 18.0 % and 26.9 versus 19.8 %, respectively; the corresponding 30-day pneumonia-specific mortality rates were 6.6 versus 6.2 %, 5.9 versus 5.6 % and 8.7 versus 7.5 % [11, 12].

What is the efficacy of ceftobiprole medocaril in community-acquired pneumonia?

Ceftobiprole medocaril was noninferior to ceftriaxone ± linezolid in terms of clinical cure rates at the TOC visit in a double-blind trial in patients with CAP requiring hospitalization and intravenous antibiotics for ≥3 days (Table 3) [8, 13]. There were no significant BGDs in clinical cure rates within subgroups of age (<65 vs. ≥65 years; <75 vs. ≥75 years), baseline Pneumonia Severity Index (PSI) score (<91 vs. ≥91) Pneumonia Patient Outcomes Research Team score (PORT) [I–V], bacteraemia (present vs. absent) and systemic inflammatory response syndrome (SIRS) [present vs. absent] in the ITT or CE population. These data indicate that ceftobiprole medocaril is effective in patients at risk for poor outcomes (i.e. age ≥75 years; PSI ≥91; PORT score IV and V; presence of bacteraemia or SIRS) [13].

Clinical cure rates for the most commonly isolated baseline pathogens in the ME population were generally similar between the treatment groups (Fig. 1b) [13]. Of note, all patients who had MDR strains of *S. pneumoniae* ($n = 2$) or *S. pneumoniae* and PSI score ≥91 ($n = 10$) at baseline achieved clinical cure with ceftobiprole medocaril. Furthermore, 12 of 16 patients who had a documented atypical pneumonia (with no typical pathogen identified) and 4 of 4 patients who had a CAP infection caused by both typical and atypical pathogen achieved clinical cure with ceftobiprole medocaril [13].

Consistent with clinical cure rates, ceftobiprole medocaril was noninferior to ceftriaxone ± linezolid in terms of microbiological eradication rates (Table 3) [13]. The clinical trial protocol allowed patients to switch to oral cefuroxime if they met certain predefined criteria after day 3 of the randomized treatment period in both groups. In patients who switched, microbiological eradication rates were significantly lower with ceftobiprole medocaril than with ceftriaxone ± linezolid (89 vs. 100 %; 95 % CI for BGD −20.8 to −0.8; $n = 37$ and 41, respectively) [13]. The reason for this finding is not clear.

During the first 30 days of treatment, one ceftobiprole medocaril recipient and three ceftriaxone ± linezolid recipients died because of pneumonia-specific causes (ITT analysis) [13].

What is the tolerability profile of ceftobiprole medocaril?

Intravenous ceftobiprole medocaril was generally well tolerated in patients with HAP [12] or CAP [13] participating in the pivotal trials. Safety was assessed in 386 patients each in ceftobiprole and comparator group in the HAP trial [12], and 310 and 322 patients, respectively, in the CAP trial [13]. The majority of patients in the ceftobiprole medocaril and comparator groups experienced at least one treatment-emergent adverse event (76 vs. 78 % in the HAP trial and 70 vs. 65 % in the CAP trial) [13, 14]. However, the incidence of treatment discontinuation because of these events was relatively low (14 vs. 10 % in the HAP trial and 6 vs. 4 % in the CAP trial) [13, 14].

In a combined analysis [8] of patients with HAP, CAP or complicated skin and soft tissue infections ($n = 1668$), the most common (incidence ≥3 %) adverse events reported with ceftobiprole medocaril (500 mg two or three times daily, or 750 mg twice daily) were nausea, vomiting, diarrhoea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity) and dysgeusia.

The incidence of treatment-related adverse events with ceftobiprole medocaril was 25 % in the HAP trial [12] and 36 % in the CAP trial [13]. The most common were hyponatraemia (4 %) and diarrhoea (3 %) in patients with HAP, and self-limited nausea (7 %) and vomiting (5 %) in those with CAP.

The incidence of serious adverse events with ceftobiprole medocaril was 36 and 11 % in the HAP [12] and CAP [13] trials, although these events were considered treatment-related only in 4 and 1 % of patients, respectively. Treatment-related serious adverse events occurring in ceftobiprole medocaril recipients in the HAP trial included four patients with hyponatraemia, two patients with coma, and one patient each with cardiac arrest, nausea, vomiting, no therapeutic response, pyrexia, hypersensitivity, bronchopneumonia, *Clostridium difficile* colitis, lung abscess, QT prolongation, increased hepatic enzymes, abnormal laboratory test, hypocalcaemia, convulsion, pulmonary oedema, respiratory distress, respiratory failure and shock. In the CAP trial, treatment-related serious anaemia, anaphylactic shock and viral infection occurred in one ceftobiprole medocaril recipient each.

In a small study in healthy volunteers, ceftobiprole medocaril had no significant ecological impact on the normal human intestinal flora, with no *C. difficile* strains or toxins detected in faecal samples [15]. However, there is a special warning regarding *C. difficile*-associated diarrhoea with the use of ceftobiprole medocaril (Table 2) [8].

What is the current positioning of ceftobiprole medocaril?

Ceftobiprole medocaril is a valuable initial empirical antibacterial option for patients with HAP (excluding VAP) or CAP. It shows broad-spectrum activity against many Gram-positive and Gram-negative bacteria that cause HAP

and CAP [11]. In vitro, ceftobiprole medocaril has low potential for resistance evolution among clinically relevant bacterial pathogens [11].

With respect to organisms associated with HAP, ceftobiprole medocaril shows potent in vitro activity against MRSA (Table 1), as well as activity against *S. aureus* strains that were resistant to vancomycin and those that are not susceptible to linezolid, the well-established anti-MRSA agents. Thus, an advantage of ceftobiprole medocaril in the treatment of HAP is that it provides coverage against MRSA. The drug also shows good in vitro activity against Enterobacteriaceae, but is susceptible to ESBL-producing strains of these organisms; therefore, the prevalence of such strains should be considered when initiating treatment with ceftobiprole medocaril. Based on a non-species specific breakpoint, ≈65 % of *P. aeruginosa* isolates were susceptible to ceftobiprole (Table 1) and, as with other cephalosporins, ceftobiprole has limited activity against *Acinetobacter* spp.

For organisms associated with CAP, ceftobiprole medocaril shows potent in vitro activity against *S. pneumoniae*, including penicillin-resistant strains of these organisms (Table 1). Of interest, penicillin resistance in *S. pneumoniae* isolates in the EU varies: in 2013, resistance was low (0–7 % of isolates) in the majority of participating countries (21 of 29 countries). However, in the remaining eight countries, resistance was evident in up to 40 % of isolates [16]. Agents used for the treatment of CAP across Europe include β-lactam antibacterials, macrolides and quinolones either alone or in combination [17]. Thus, ceftobiprole medocaril represents an extension to the currently available options for CAP. A potential limitation of ceftobiprole medocaril is that it requires intravenous administration over a period of 2 h every 8 h.

In pivotal clinical trials, intravenous ceftobiprole medocaril was effective and well tolerated in patients with HAP (excluding VAP) and in hospitalized patients with CAP (including those at risk for poor outcomes). It was noninferior to ceftazidime + linezolid for the treatment of HAP and to ceftriaxone ± linezolid for the treatment of CAP. The use of ceftobiprole medocaril monotherapy may simplify initial empirical treatment relative to the use of combination therapies in these patient populations.

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