

## Resubmission:

ceftobiprole, 500mg, powder for concentrate for solution for infusion (Zevtera<sup>®</sup>)  
SMC No. (943/14)

### Basilea Pharmaceutica International Ltd

05 June 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**ceftobiprole (Zevtera<sup>®</sup>)** is accepted for restricted use within NHS Scotland.

**Indication under review:** Ceftobiprole is indicated for the treatment of the following infections in adults:

- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

**SMC restriction:** for use in the treatment of HAP (excluding VAP) when activity is required against suspected methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative pathogens (including *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*) and when combination treatment that includes vancomycin or teicoplanin is inappropriate or has not been tolerated, or when treatment modification is required, i.e. as an alternative to linezolid-based regimens.

In a randomised, double-blind phase III study of patients with HAP, the clinical cure rate for empirical treatment with ceftobiprole was non-inferior to the rate associated with intravenous linezolid plus an anti-pseudomonal cephalosporin.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

Published 13 July 2015

## Indication

Ceftobiprole is indicated for the treatment of the following infections in adults:

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- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

## Dosing Information

The recommended dose is 500mg administered as a two-hour intravenous infusion every eight hours. For CAP, a switch to an appropriate oral antibiotic may be considered after completion of at least three days of intravenous ceftobiprole medocaril sodium treatment, depending on the patient's clinical response.

## Product availability date

29th April 2015

## Summary of evidence on comparative efficacy

Ceftobiprole (as medocaril sodium) is a new intravenous (IV) cephalosporin with activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae*, and Gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*.<sup>1</sup>

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers ceftobiprole when positioned for use in the treatment of hospital-acquired pneumonia (HAP) when activity is required against suspected methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative pathogens (including *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*) and when combination treatment that includes vancomycin or teicoplanin is inappropriate, has not been tolerated, or treatment modification is required, i.e. as an alternative to linezolid-based regimens.

The clinical evidence derives from a multi-centre, randomised, double-blind, phase III, non-inferiority study which recruited adults with a clinical diagnosis of pneumonia after at least 72 hours of hospitalisation or stay in a clinical care facility.<sup>2</sup> Patients had to have clinical signs or symptoms of pneumonia and at least two of: tachypnoea, hypoxaemia or purulent respiratory secretions; fever or leucocytosis/leucopenia; new or persistent radiographic infiltrates; and an Acute Physiology and Chronic Health Evaluation II (APACHE II) prognostic score between 8 and 25.

Patients were randomised equally to IV infusions of ceftobiprole 500mg every eight hours plus placebo every 12 hours (n=391), or ceftazidime 2g every eight hours plus linezolid 600mg every 12 hours (n=390). Treatment was planned for seven to 14 days. Additional open-label fluoroquinolone or aminoglycoside was permitted for patients at risk of pseudomonal infection. Randomisation was stratified by HAP sub-type (ventilator-associated pneumonia [VAP] or HAP but not VAP) and by APACHE II scores (8 to 19 versus 20 to 25).

The primary outcome was clinical cure, defined as resolution of signs and symptoms of infection, or improvement to the extent that no further antimicrobial therapy was indicated. This was assessed at the test-of-cure visit (at 7-14 days post end-of-treatment) in the two co-primary datasets: intention-to-treat (ITT) and clinically evaluable (CE). The ITT population included all randomised patients, whereas the CE population was defined as all patients who received at least one dose of study medication and who were clinically evaluable at the test of cure visit. The study was designed to test for non-inferiority, with a pre-defined margin of 15%. Major secondary endpoints included 30-day all-cause or pneumonia-specific mortality and microbiological eradication.

In the total study population (all types of HAP), ceftobiprole was demonstrated to be non-inferior to linezolid plus ceftazidime in both the ITT and CE datasets. The sub-group of patients which represents the licensed population are those with a diagnosis of HAP but not VAP (n=571). In the HAP but not VAP sub-group, ceftobiprole was also demonstrated to be non-inferior to linezolid plus ceftazidime in both datasets. The clinical cure rates and secondary outcomes for this licensed population are presented in the table below.<sup>2</sup>

		<b>Ceftobiprole, proportion (n/N)</b>	<b>Ceftazidime plus linezolid, proportion (n/N)</b>	<b>Between treatment difference (95% CI)</b>
Clinical cure (ITT)		60% (171/287)	59% (167/284)	0.8% (-7.3 to 8.8)
Clinical cure (CE)		78% (154/198)	76% (141/185)	1.6% (-6.9 to 10.0)
30-day all-cause mortality (ITT)		17%	18%	-1.2% (-7.4 to 5.0)
30-day pneumonia-specific mortality (ITT)		5.9%	5.6%	0.3% (-3.5 to 4.1)
Microbiological eradication	mITT	49% (87/179)	54% (97/181)	-5.0% (-15.3 to 5.3)
	ME	63% (73/116)	68% (81/120)	-4.6% (-16.7 to 7.6)

Table: Outcomes in the licensed sub-group (HAP but not VAP).<sup>2</sup>

CI = confidence interval.

mITT = ITT patients with a valid pathogen at baseline.

ME = all patients in the CE dataset with a valid pathogen at baseline and microbiologically evaluable at the test of cure visit.

In the 38 patients in the microbiologically evaluable dataset who had MRSA, the clinical cure rate was 68% (13/19) for ceftobiprole and 63% (12/19) for ceftazidime plus linezolid. The clinical cure rates for ceftobiprole and ceftazidime plus linezolid respectively, for selected Gram negative pathogens were: *Escherichia coli* (57% [8/14] versus 64% [7/11]), *Klebsiella pneumonia* (92% [11/12] versus 79% [15/19]) and *Pseudomonas aeruginosa* (75% [12/16] versus 70% [14/20]).

## Summary of evidence on comparative safety

Treatment-related adverse events (AE) were reported in 25% (96/386) of ceftobiprole patients and 25% (98/386) of ceftazidime plus linezolid patients. AEs resulted in discontinuation from the study in a low proportion of patients: 3.6% (14/391) in the ceftobiprole group, and 1.5% (6/390) in the ceftazidime plus linezolid group.

The most commonly reported treatment-related AE were: diarrhoea (ceftobiprole 3.1%, ceftazidime plus linezolid 6.5%) and hyponatraemia (4.4% and 2.6% respectively).<sup>2</sup>

Eight patients (n=4 [1.0%] in each treatment group) had a treatment-related death in the study. All of these patients had significant co-morbidities.<sup>3</sup>

A class warning regarding *Clostridium difficile*-related colitis is included in the prescribing information for ceftobiprole.<sup>1</sup> Ceftobiprole is a cephalosporin, and the risk of *C. difficile* colitis and relevant prescribing guidelines would need to be taken into account with its use. There is a risk of hypersensitivity reactions in patients with a history of hypersensitivity to beta-lactam antibacterials.

## Summary of clinical effectiveness issues

Ceftobiprole is a new cephalosporin licensed for the treatment of HAP (excluding VAP) and CAP. It is active against Gram-positive bacteria, including MRSA and Gram-negative bacteria, including *Escherichia coli* and *Klebsiella pneumoniae*. The submitting company has requested that the SMC considers ceftobiprole when positioned for use in the treatment of HAP when activity is required against suspected MRSA and Gram-negative pathogens (including *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*), and when combination treatment that includes vancomycin or teicoplanin is inappropriate or has not been tolerated, or when treatment modification is required.

Clinical experts consulted by SMC have advised that in the management of HAP where MRSA is suspected or proven, regimens combining vancomycin, teicoplanin or linezolid with antibiotics with Gram-negative coverage are used. Antibiotic regimens with Gram-negative cover recommended in Scotland include: piperacillin-tazobactam, amoxicillin plus aztreonam, levofloxacin, and co-amoxiclav plus gentamicin.

The study recruited a broader population of patients to those who would be eligible for ceftobiprole within its licensed indication. The sub-group with HAP (no VAP) accounted for 73% of the full study population. Baseline characteristics of patients in this sub-group were well balanced, with the exception of gender (greater proportion of males in the ceftobiprole group compared with the control group) and despite lower power, non-inferiority was demonstrated in this sub-group.

Patients were not specifically recruited to the study on suspicion of having MRSA and/or Gram-negative pathogens, nor on the grounds of vancomycin or teicoplanin being inappropriate. The clinical effectiveness of ceftobiprole in this specific group of patients is unknown.

To support the economic case, a Bayesian network meta-analysis (NMA) was conducted to allow comparisons of the clinical effectiveness of ceftobiprole with that of relevant comparators for the empirical management of HAP (meropenem, piperacillin-tazobactam, imipenem, ceftazidime and fluoroquinolones). The network of evidence included 11 studies; one had a linezolid-containing treatment group (the ceftobiprole phase III study described above). Endpoints compared were clinical response, all-cause-mortality, AEs, drug-related AEs, or discontinuation due to drug-related AEs. Multiple models were used in the analysis: random-effects with vague priors, random-effects with Turner's informative prior, and fixed-effects. The analysis found insufficient evidence of differences between ceftobiprole versus comparators for the outcomes compared. While credible intervals were wide enough to draw this conclusion, the odds ratios for specific comparisons suggested there may be differences if there was less uncertainty. Treatments were also ranked for each outcome based on the probability that each was the best treatment.

Due to the analysis comparing outcomes in patients with all types of HAP (not specifically non-VAP HAP), and the lack of comparison with linezolid-containing regimens, the relevance of the analysis to the company's proposed positioning of ceftobiprole and to the economic case is uncertain. There are limitations which may reduce the internal validity of the NMA. Treatment arms of ceftazidime containing regimens were combined in order to construct a network of evidence; i.e. for the "ceftazidime" node; ceftazidime plus linezolid, ceftazidime plus tobramycin, and ceftazidime plus amikacin were combined. The same was true for piperacillin-tazobactam containing regimens. A further limitation is that nearly half the studies recruited patients with other serious infections and not just patients with HAP. There are therefore a number of limitations with the NMA based on the limited evidence base and there is some uncertainty about the assumption of similar efficacy.

Ceftobiprole may have an advantage over combination antibacterial regimens in terms of the number of IV infusions required over the treatment course.

Prescribing of cephalosporins in Scotland is severely restricted due to the potential for *Clostridium difficile* infection. If ceftobiprole was to be introduced, then its use would be subject to antimicrobial prescribing policies and antibacterial stewardship.

## Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing ceftobiprole with linezolid in combination with piperacillin-tazobactam, meropenem, ciprofloxacin, moxifloxacin, levofloxacin, gentamicin or ceftazidime for the treatment of HAP (excluding VAP) patients when activity is required against suspected MRSA and Gram-negative pathogens, or when combination treatment that includes vancomycin or teicoplanin is inappropriate or has not been tolerated, or when treatment modification is required. While a range of comparator regimens were included in the analysis, in the base case, the comparison was against a weighted average of linezolid + piperacillin-tazobactam and linezolid + meropenem. The time horizon used in the analysis was 7 days (duration of a course of antibiotic treatment). Expert responses have indicated that the comparators included in the analysis are likely to be the displaced treatments in Scotland.

The clinical data used to support the cost-minimisation analysis were taken from the NMA noted above which evaluated the efficacy and safety of ceftobiprole compared with ceftazidime, meropenem, imipenem-cilastatin, piperacillin-tazobactam, ciprofloxacin and levofloxacin. A number of outcomes including clinical response, AEs and all cause mortality were assessed. Based on the results of the analysis, no evidence of a significant difference was identified versus the comparators. It should be noted that a phase III randomized controlled study versus linezolid plus ceftazidime was also provided which demonstrated non-inferiority for ceftobiprole versus linezolid plus ceftazidime, with comparable cure rates (60% vs. 59% respectively). Results of the economic analysis are dependent on the assumption of comparable efficacy from the NMA.

Drug acquisition costs and administration costs were included in the analysis. Ceftobiprole was associated with a lower number of administrations compared with piperacillin-tazobactam (3 vs. 4 per day respectively) and the same number of administrations compared to meropenem (3 administrations per day). Administration costs associated with IV linezolid were also included; however, in the base case analysis the company assumed a proportion of patients would switch to oral linezolid after initiation with IV linezolid. Monitoring costs were included for linezolid and gentamicin treatments.

In the base case analysis, ceftobiprole was estimated to result in a total treatment cost of £914.38 versus £1,106.24 for the weighted average comparator of linezolid plus piperacillin-tazobactam,

resulting in total savings of £191.86 with ceftobiprole. Total savings consisted of drug cost savings of £144.66 and administration and monitoring savings of £47.20.

The company included a number of scenario analyses which tested a range of assumptions including extension of treatment duration to 14 days, reduced administration costs for linezolid, increased proportion of patients receiving oral linezolid and a weighted average versus all comparators.-ceftobiprole remained cost saving in all scenarios. However, it should be noted that based on a comparison versus linezolid plus gentamicin alone, ceftobiprole is no longer cost saving, resulting in an incremental cost per treatment of £186.77.

The following limitations were identified:

- The key weakness relates to the lack of comparison with linezolid-containing regimens within the NMA. As the economic analysis presents the results versus linezolid regimens, the NMA may not be appropriate to inform the cost-minimisation analysis. Furthermore, results have not been presented separately for the subgroup of patients with HAP (excluding VAP) and as such the results may not adequately reflect the revised positioning within this resubmission. Due to these weaknesses, the assumption of comparable efficacy versus these treatments is uncertain.
- Compared with linezolid plus gentamicin, ceftobiprole is expected to result in a cost of £186.77 based on incremental drug costs of £150.08 and incremental administration and monitoring cost of £36.69. However this analysis may not be a major concern as gentamicin does not appear to be the treatment most widely used in Scotland.

On balance, despite these limitations, the economic case has been demonstrated.

## Summary of patient and public involvement

A Patient Group submission was not made.

## Additional information: guidelines and protocols

In December 2014, the National Institute for Health and Care Excellence (NICE) published clinical guideline 191, "Pneumonia: diagnosis and management of community- and hospital-acquired pneumonia in adults".<sup>4</sup> HAP was defined as pneumonia which develops  $\geq 48$  hours after hospital admission and that was not incubating at admission. VAP was excluded from the scope of the guidance. Hospital acquired infections can be caused by highly-resistant pathogens that require treatment with extended-spectrum antibiotics as recommended by the British Society of Antimicrobial Chemotherapy (BSAC) guidance.

Recommendations from NICE included:

- Antibiotic therapy should be offered at the earliest opportunity, within four hours of diagnosis of HAP.
- The choice of therapy should be guided by local hospital policy and the clinical circumstances of the patient. The policies should reflect knowledge of local microbial pathogens.
- A treatment duration between five and ten days for HAP.

The British Society for Antimicrobial Chemotherapy published "Guidelines for the management of hospital-acquired pneumonia (HAP) in the UK" in 2008.<sup>5</sup> These recommend that:

- "The choice of empirical antibiotic therapy of patients with HAP in an individual unit should be based on the knowledge of the nature and susceptibility patterns of pathogens that are prevalent

on that unit and should also take account of such variables as duration of hospital stay (i.e. early- or late-onset infection), recent administration of antibiotic therapy and co-morbidities. Similarly, definitive therapy should be determined by culture and susceptibility test results”.

- “For patients with early-onset infections (fewer than 5 days following admission to hospital) who have not previously received antibiotics and in the absence of other risk factors, the use of co-amoxiclav or cefuroxime would be appropriate.”
- “For patients with early-onset infections... who have recently received antibiotics and/or who have other risk factors, a third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone or piperacillin/tazobactam would be appropriate.”

With respect to specific pathogens of interest to the proposed positioning of ceftobiprole the guidelines note that:

- “there is no proven optimal antibiotic regimen for patients with HAP suspected or proven to be caused by *Pseudomonas aeruginosa*. Treatment options include ceftazidime, ciprofloxacin, meropenem and piperacillin/tazobactam.”
- “no firm conclusion can be reached on the use of linezolid or a glycopeptides as optimal treatment of patients with HAP or VAP caused by MRSA.”

## Additional information: comparators

Various regimens of antibiotics are recommended in Health Board empirical antibiotic guidelines including: piperacillin-tazobactam, amoxicillin plus aztreonam, levofloxacin (usually as an option if penicillin allergy), and co-amoxiclav plus gentamicin. In cases where MRSA is suspected or proven, glycopeptides (vancomycin or teicoplanin) are added. Linezolid is often reserved for second-line use after glycopeptides.

## Cost of relevant comparators

Drug	IV Dose Regimen	Cost per course (£)
<b>ceftobiprole</b>	<b>500mg every 8 hours</b>	594 to 1,189
Linezolid	600mg twice daily	445 to 890
amoxicillin + aztreonam	1g every 8 hours 2g every 8 hours	299 to 597
levofloxacin	500mg twice daily	264 to 528
piperacillin-tazobactam	4.5g every 8 hours*	237 to 474
meropenem	500mg to 1g every 8 hours	155 to 310
co-amoxiclav + gentamicin	1.2g every 8 hours 5mg/kg every 24 to 48 hours	41 to 82

Doses are for general comparison and do not imply therapeutic equivalence. Antibiotics are likely to be prescribed in combination and are those noted by clinical experts consulted by SMC. Costs are for a five to 10-day course (as recommended in NICE guidance) and based on 70kg body weight. Costs from eVadis (April 2015) except ceftobiprole (company’s submission). \*Dose as per empirical antibiotic guidelines from several Health Boards.

## **Additional information: budget impact**

The estimated number of patients assumed eligible for treatment is 431 in each year, with an estimated uptake rate of 10% in year 1, rising to 50% in year 5. The gross impact on the medicines budget was estimated to be £36k in year 1, rising to £180k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to result in savings of £8k in year 1 and £41k in year 5.



## References

The undernoted references were supplied with the submission.

1. Basilea Pharmaceutical International Ltd. Summary of product characteristics - Zevtera 500 mg powder for concentrate for solution for infusion. [cited 8<sup>th</sup> April 2015]; available from [www.medicines.org.uk](http://www.medicines.org.uk)
2. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, *et al.* A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America.* 2014;59(1):51-61.
3. MHRA. Public Assessment Report: Decentralised Procedure – Zevtera 500mg powder for concentrate for solution for infusion (Ceftobiprole medocaril sodium) PL 32205/0003. [cited 8 April 2015]; available from [www.mhra.gov.uk](http://www.mhra.gov.uk)
4. National Institute for Health and Care Excellence (NICE). Clinical guideline no191. Pneumonia: diagnosis and management of community- and hospital-acquired pneumonia in adults. 2014. [cited 8<sup>th</sup> April 2015]; available from <https://www.nice.org.uk/>
5. British Society for Antimicrobial Chemotherapy (BSAC). Guidelines for the management of hospital-acquired pneumonia in the UK; report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother.* 2008;62(1):5-34.

This assessment is based on data submitted by the applicant company up to and including 15 May 2015.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

### **Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*