



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Ceftobiprole medocartil sodium

Proprietary Product Name: Zevtera

Sponsor: JACE Pharma Australia

February 2016

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AE	Adverse event
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AIDS	Acquired immunodeficiency syndrome
AM	Alveolar macrophages
ANC	Absolute neutrophil count
ARF	Acute renal failure
APACHE II	Acute Physiology Score and Chronic Health Evaluation II
AUC	Area under the plasma concentration–time curve
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero to infinity
AUC _{0-8h}	Area under the plasma concentration-time curve over the time interval 0 to 8 h
AUC _{ss24h}	AUC over a 24 hr period at steady state
AUIC	Area under the inhibition curve
BID	Twice a day
BLQ	Below the limit of quantification
BP	Blood pressure
CAP	Community-acquired pneumonia
CDAD	Clostridium difficile associated diarrhoea
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Plasma clearance
CLR	Total renal clearance, estimated by $CL_S \times f_u$, where f_u is the fraction of

Abbreviation	Meaning
	dose excreted in urine within 24 h.
CL _s	Is the total systemic clearance estimated by $CL_s = \text{dose}/AUC_{0-\infty}$.
C _{max}	Is the observed maximum plasma concentration
C _{min}	Minimum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
C _p	Plasma concentration
CrCl	Creatinine clearance
CK	Creatine kinase
cSSSI	Complicated skin and skin structure infection
DAGT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
DIIHA	Drug-induced immune haemolytic anaemia
DSUR	Development safety update report
ECG	Electrocardiogram
ELF	Epithelial lining fluid
EMA	European medicines agency
EOI	End of infusion
EOT	End of therapy
ESBL	Extended spectrum β-lactamases
ESRD	End-stage renal disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EU	European union
EU-RMP	European union risk management plan
EU-QPPV	EU Qualified Person for Pharmacovigilance
FBC	Full blood count

Abbreviation	Meaning
gp	Group
GPU	Global Pharmacovigilance Unit
HAP	Hospital-Acquired Pneumonia
Hb	Haemoglobin
FDA	Food And Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference On Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
ISR	Infusion/Injection Site Reaction
IV	Intravenous
LC/LC-MS/MS	Gradient Reversed-Phase Liquid Chromatography In Back-Flush Mode Coupled With A Tandem Mass Spectrometer
LL	Lower Limit
LRTI	Lower Respiratory Tract Infection
MAA	Marketing Authorization Application
MCS	Monte Carlo Simulation
MDR	Multi-Drug Resistant
MEDRA	Medical Dictionary For Regulatory Activities
MIC	Minimum Inhibitory Concentration
ml	Milliliters
MRSA	Methicillin-Resistant Staphylococcus Aureus
MSSA	Methicillin-Susceptible Staphylococcus Aureus
NAFLD	Non-Alcoholic Fatty Liver Disease
NIDDM	Non-Insulin Dependent Diabetes Mellitus

Abbreviation	Meaning
NOAEL	No-Observed Adverse- Effect Level
NP	Nosocomial Pneumonia
PBPs	Penicillin Binding Proteins
PD	Pharmacodynamic
PI	Prescribing Information
PK	Pharmacokinetic
pKa	Acid Dissociation Constant
PMS	Post Marketing Surveillance
PORT	Pneumonia Outcomes Research Team
PRSP	Penicillin-Resistant Streptococcus Pneumoniae
PSI	Pneumonia Outcomes Research Team Severity Index
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTA	Probability Of Target Attainment
QD	Once Daily
RMP	Risk Management Plan
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SIRS	Systemic Inflammatory Response Syndrome
SmPC	Summary Of Product Characteristics
SMR	Standardised Mortality Rate
SOC	System Organ Class
SOP	Standard Operation Procedure

Abbreviation	Meaning
tds	Three Times A Day
TEAE	Treatment-Emergent AE
TRAE	Treatment-Related AE
$t_{1/2b}$	Apparent Terminal Elimination Half-Life
TOC	Test-Of-Cure
UL	Upper Limit
ULN	Upper Limit Of Normal
US	United States
VAP	Ventilator-Associated Pneumonia
VRSA	Vancomycin-Resistant <i>Staphylococcus Aureus</i>
V_{ss}	Volume Of Distribution
WBC	White Blood Count

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	2 November 2015
<i>Date of entry onto ARTG</i>	10 November 2015
<i>Active ingredient(s):</i>	Ceftobiprole medocaril sodium
<i>Product name(s):</i>	Zevtera
<i>Sponsor's name and address:</i>	JACE Pharma Pty Ltd 7 Clunies-Ross Court, Brisbane Technology Park Eight Mile Plains, QLD, 4113
<i>Dose form(s):</i>	Powder for Injection
<i>Strength(s):</i>	667 mg (equivalent to 500 mg ceftobiprole)
<i>Container(s):</i>	20 mL vials
<i>Pack size(s):</i>	10 vials
<i>Approved therapeutic use:</i>	<p><i>Zevtera (ceftobiprole medocaril sodium) is indicated for the treatment of the following infections in adults suspected or proven to be caused by designated susceptible microorganisms:</i></p> <ul style="list-style-type: none">• <i>Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)</i>• <i>Community-acquired pneumonia (CAP)</i>
<i>Route(s) of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	<p>Zevtera must be reconstituted and then further diluted (see Special precautions for disposal and other handling) prior to administration by intravenous infusion over a period of 2 hours.</p> <p><i>Adults (18 years and older)</i></p> <p>The recommended dose of Zevtera is 666.6 mg administered as a 2-hour intravenous infusion every 8 hours. Treatment is continued for 4-14 days depending on disease severity and patient response. For CAP, a switch to an appropriate oral antibiotic may be considered after completion of at least 3 days of intravenous ceftobiprole medocaril sodium treatment, depending on the patient's clinical response.</p> <p><i>Children (<18 years)</i></p>

The safety and efficacy of Zevtera in children aged birth to < 18 years have not yet been established. Zevtera is not recommended for use in children or adolescents below 18 years of age.

Elderly

No dose adjustment is necessary in elderly patients, except in cases of moderate to severe renal impairment (see below [PI] and Pharmacokinetic Properties).

ARTG number (s): 229773

Product background

This AusPAR describes the application by JACE Pharma Pty Ltd, acting as an agent for Basilea Pharmaceutica International Ltd, to register the new chemical entity ceftobiprole medocaril sodium as Zevtera for the treatment of infections in adult patients with hospital-acquired pneumonia (excluding ventilator-associated pneumonia) or community-acquired pneumonia (CAP).

Ceftobiprole medocaril sodium was developed as a prodrug, due to solubility limitations of the active moiety ceftobiprole. Ceftobiprole medocaril sodium is a beta-lactam antibiotic with bactericidal activity against a broad spectrum of gram positive and negative bacteria; many of these are important aetiological agents of CAP and/or nosocomial pneumonia. As with other cephalosporins, ceftobiprole acts by binding tightly to penicillin binding proteins (PBPs). PBPs are membrane associated bacterial enzymes involved in cell wall biosynthesis. Ceftobiprole binds tightly to the PBPs related to beta-lactam resistance in staphylococci (PBP2a) and pneumococci (PBP2x). At this juncture, there appears to be a low propensity for the development of resistance.

Ceftobiprole can be considered a 'fifth generation' cephalosporin as its antibacterial activity extends to methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA), vancomycin-resistant *S. aureus* (VRSA), as well as penicillin-resistant *Streptococcus pneumoniae* (PRSP) and ceftriaxone-resistant *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catharralis*, *enterobacteriaceae* and *Pseudomonas aeruginosa*.

Regulatory status

This is an application for a new chemical entity. The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on the 10 November 2015.

For the treatment of hospital-acquired pneumonia (HAP) and community-acquired pneumonia CAP), an application was made by Basilea Medical UK in 2012 via the decentralised route with United Kingdom (UK) as the reference member state. Marketing authorisation was granted in the UK for the treatment of HAP and CAP on 20 November 2013 (Table 1). Following approval under the European decentralized procedure, ceftobiprole medocaril has received national licenses for the treatment of CAP and HAP (excluding VAP) in adults in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Norway, Spain and Sweden. A similar application has been approved in Switzerland and Canada (Table 1).

Table 1: International regulatory status

Country	Invented Name/ Active substance	Dosage Form/ Strength	Indication(s)	Approval Date
UK ¹	Zevtera/ Ceftobiprole	Powder for concentrate for solution for infusion 500 mg	Hospital-acquired pneumonia (HAP), excluding ventilator- associated pneumonia (VAP) Community- acquired pneumonia (CAP)	20 Nov 2013
Switzerland	Zevtera/ Ceftobiprole	Powder for concentrate for solution for infusion 500 mg	Hospital-acquired pneumonia (HAP), excluding ventilator- associated pneumonia (VAP) Community- acquired pneumonia (CAP)	23 Dec 2014
Canada	Zevtera/ Ceftobiprole	Powder for concentrate for solution for infusion 500 mg	Hospital-acquired pneumonia (HAP), excluding ventilator- associated pneumonia (VAP) Community- acquired pneumonia (CAP)	24 Sep 2015

¹Decentralised Procedure: Reference Member State.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

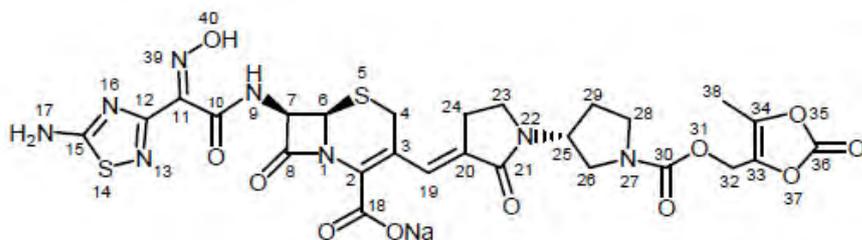
Introduction

Drug substance (active ingredient)

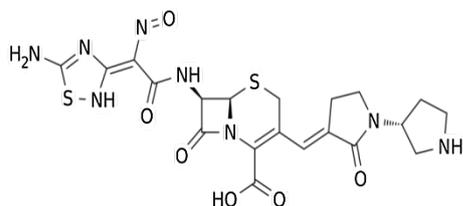
The new chemical entity ceftobiprole medocaril sodium is a powder for injection, containing 667 mg of the drug substance in vials. The drug substance is a pro-drug for the cephalosporin beta-lactam antibiotic ceftobiprole (Figure 1) and the proposed product contains the equivalent of 500 mg of the active antibiotic. Use of the prodrug is necessary to overcome the very low solubility of ceftobiprole itself.

The strength of the proposed product was initially expressed on the labels and elsewhere with respect to the quantity of the active antibiotic metabolite ceftobiprole (500 mg). This was not considered appropriate nor consistent with TGA practice and the company has now submitted labelling with respect to the prodrug (that is, ceftobiprole medocaril sodium 667 mg).

Figure 1: Chemical structures of ceftobiprole medocaril sodium and ceftobiprole



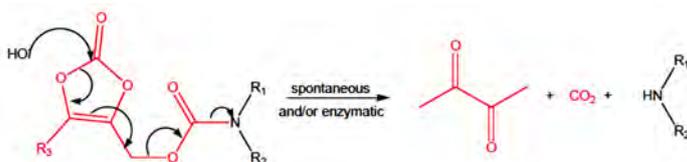
Ceftobiprole medocaril sodium



Ceftobiprole

As shown below (Figure 2), the (oxodioxolenyl) methyl carbamate (that is, medocaril) moiety of the drug substance undergoes *in vivo* cleavage, by base or enzyme catalysis to form ceftobiprole free amine and releasing butanedione (aka diacetyl) and carbon dioxide (CO₂). Analogous pro-drugs which cleave in a similar manner are preceded on the ARTG (such as Olmesartan medoxomil).

Figure 2: Cleavage of (oxodioxolenyl)methyl carbamate moiety (medocaril) to give the free amine



Ceftobiprole medocaril sodium is a white to yellowish or slightly brownish amorphous, hygroscopic powder which is highly soluble in water and at higher pH (>60 mg/mL), but solubility drops below pH 4 (for example, 2 mg/mL at pH 3). It is sparingly soluble in

propylene glycol and insoluble in many other organic solvents (such as acetonitrile, acetone and tetrahydrofuran (THF)).

Ceftobiprole medocaril sodium is manufactured in 6 chemical steps and the process is considered adequately described and controlled. A large number of potential related substances were identified, resulting from the fermentation and chemical steps and 21 of these are controlled as specified impurities in the drug substance.

Controls applied to the drug substance are considered acceptable after some tightening of limits for some specified impurities, in-line with the provided toxicological justification.

Drug product

Zevtera is a sterile lyophilised powder for concentrate for solution for infusion containing ceftobiprole medocaril in a sodium citrate buffer system. The finished dosage form contains 666.6 mg of ceftobiprole medocaril sodium, 26.3 mg of citric acid monohydrate and approximately 10 mg sodium hydroxide (for pH adjustment) as a lyophilised powder in a 20 mL Type I glass vial with a fluoropolymer-coated bromobutyl stopper.

The product must be reconstituted and then further diluted prior to infusion. Prior to reconstitution, the product appears as a *yellowish to slightly brown powder or cake*.

The reconstituted solution is a *clear to a slightly opalescent, yellowish to brownish solution free from visible foreign material*. Each vial is reconstituted with 10 mL of either water for injection or 5% glucose injection to yield 66.7 mg/mL of ceftobiprole medocaril (equivalent to 50.0 mg/mL ceftobiprole), prior to further dilution with the intravenous infusion solution (infusion bag or bottle containing 250 mL of 0.9% sodium chloride, 5% dextrose, or lactated Ringer's solutions for injection).

The recommended dose of Zevtera is 500 mg (as 667 mg ceftobiprole medocaril sodium) administered as a 2 h intravenous infusion every 8 h (that is, 2000 mg of ceftobiprole medocaril sodium per day). Treatment is continued for 4 to 14 days depending on disease severity and patient response.

The drug substance is very soluble in aqueous media at pH > 4 but rapidly decomposes in non-acidic media pH > 6, mainly to the active drug ceftobiprole. Consequently, a citrate buffering system is necessary during manufacture of the bulk solution to ensure stability of the drug substance (pH 4.6 to 5.2). Each vial contains 26.3 mg of citric acid and the pH is adjusted with sodium hydroxide.

The product is manufactured by aseptic sterile filtration of the bulk solution followed by filling into 20 mL clear Type I glass vials and lyophilisation. The vials are sealed with fluorinated polymer coated grey bromobutyl rubber stoppers with aluminium foil crimp seal with plastic flip-off cap.

The proposed finished product specifications included controls on appearance, identity of drug substance, water content, uniformity of dosage units, reconstitution time, colour and turbidity of solution, pH, particulate matter, assay of active drug, nine degradation products, residual solvents, endotoxins and microbial limits. Apart from the proposed limits for the degradation products, these were adequately justified and comply with TGA requirements.

Toxicological data were submitted to qualify the proposed degradant limits but the nonclinical evaluator found that many limits were not adequately qualified. The company subsequently proposed lower limits for the degradants which are in-line with the toxicological assessment. The revised finished product specifications are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

However, the tightened limits for degradants necessitated a reduction of the proposed shelf-life from 48 months to 12 months (*stored at 2°C to 8°C, protected from light, do not freeze*) to ensure compliance.

There are no clinical objections to the proposed trade name.

Quality summary and conclusions

All issues raised during the initial evaluation of this application have now been satisfactorily resolved.

Microbiological aspects of the submission have been evaluated separately and all issues raised have been resolved.

Registration of the proposed Zevtera ceftobiprole medocaril sodium 667 mg powder for injection in vials is recommended with respect to quality and biopharmaceutical aspects.

As no significant pharmaceutical chemistry issues were identified, the submission was not referred to the Pharmaceutical Subcommittee of the TGA's Advisory Committee on Prescription Medicines (ACPM).

III. Nonclinical findings

Introduction

The sponsor has submitted a high quality dossier of studies. The crucial genotoxicity, repeat-dose toxicity and reproductive and developmental toxicity studies were performed to Good Laboratory practice (GLP) standard. The newly submitted studies provide useful information and cover deficiencies in the original presentation.

Pharmacology

Primary pharmacology

The sponsor's Summary of Clinical Pharmacology gave a summary of in vitro and in vivo studies testing the activity of ceftobiprole against Gram positive and negative bacteria. These studies include the testing of over 10,000 historical clinical isolates from the Europe, America, and the rest of the world for their susceptibility to ceftobiprole.

The sponsor submitted an Australian antibiotic resistance risk assessment (Risk Assessment of Microbial Resistance), including resistance of Australian bacterial isolates to ceftobiprole.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic pharmacology studies were presented by the sponsor. This is not unreasonable given the lengthy history of development and use of beta lactam type antibiotics.

No new safety pharmacology studies were submitted by the sponsor. Previously evaluated studies consisted of central nervous system (CNS) and renal studies in mice, cardiovascular studies in rats, dogs and marmosets, and a study on pulmonary function in rats. A ceftobiprole medocaril dose of ≥ 250 mg/kg IV produced tremors and convulsions in mice. The maximum plasma concentration of ceftobiprole at 250 mg/kg (183 $\mu\text{g/mL}$) was approximately 5 times the clinical concentration. Direct administration of ceftobiprole

into the mouse brain produced convulsions with similar potency to the beta lactam antibiotic imipenem (50% effective dose (ED₅₀) values of 2.55 and 3.16 µg for ceftobiprole and imipenem, respectively). These results suggest that ceftobiprole has limited ability to cross the blood-brain barrier but can induce convulsions when present at high systemic concentrations. The induction of convulsions in animals and humans is a well-known class effect of beta lactam antibiotics.¹

The cardiovascular studies showed no safety signals. Ceftobiprole showed no significant in vitro inhibition of mammalian potassium (hERG) channels, although (due to solubility issues) the drug concentration tested (5 µM) is only about a tenth of the expected clinical plasma concentration. Ceftobiprole medocaril doses of up to 500 mg/kg IV (expected to produce around 5 times the clinical concentration of ceftobiprole) showed no effects on breathing parameters. The major adverse findings from the safety pharmacology studies were renal toxicity and convulsions in mice (similar results seen for rat repeat-dose toxicity studies; see below).

Pharmacokinetics

General

New studies compared the pharmacokinetics of ceftobiprole medocaril, ceftobiprole and BAL1029 (the major metabolite of ceftobiprole, derived by beta-lactam ring opening) in rats and dogs following a single 4 h IV infusion of ceftobiprole medocaril. In both species, the pharmacokinetics was similar for both genders. Exposure (based on the area under the plasma concentration versus time curve (AUC)) to ceftobiprole was approximately 6 (rats) or 2 times (dogs) that for ceftobiprole medocaril, whilst exposure to BAL1029 was approximately one fifth (1/5) that for ceftobiprole medocaril in both species.

Distribution

Notable findings from previously presented studies using mice and rats, were the high level of ceftobiprole (and/or metabolites) uptake by kidney (both species) and the persistence of this material in kidney cortex (rat only). Such results are consistent with the renal drug precipitation and toxicity found in repeat-dose studies (see below).

Metabolism

Previously presented studies suggested that ceftobiprole was not extensively metabolised and was predominantly excreted in urine as the parental compound. A new study examined enzymes likely involved in the conversion of the ester prodrug to the active agent. It was concluded that multiple hydrolytic enzymes as well as non-enzymatic hydrolysis contribute to the conversion of ceftobiprole medocaril to ceftobiprole. Hence, pro-drug conversion is unlikely to be significantly affected by drug-drug interactions or by genetic polymorphisms that inactivate individual hydrolytic enzymes.

Conclusion

Previously reviewed studies indicated that metabolite profiles are qualitatively similar and the major route of excretion (renal) is the same between humans and tested animal species. This suggests that the animal species used provide reasonable models for the assessment of ceftobiprole medocaril toxicity in humans.

Pharmacokinetic drug interactions

In vitro studies suggested that ceftobiprole (0.3 to 200 µM) is not a substrate or inhibitor of P-glycoprotein, breast cancer resistance protein (BCRP) and multidrug resistance protein 2 (MRP2). Ceftobiprole is also not a substrate for BSEP (bile salt export pump).

¹Schliamsner S.E., Cars O. and Norrby S.R. (1991) Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. *Journal of Antimicrobial Chemotherapy*, 27: 405–425.

Ceftobiprole was, however, an inhibitor of organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3) mediated uptake of oestradiol by cultured cells with 50% inhibitory concentration (IC₅₀) values of 67.7 and 44.1 μ M, respectively (other cephalosporins have been shown to be substrates of these two transporters²). Hence, plasma levels of ceftobiprole in patients (approximately 60 μ M) could inhibit the metabolism/clearance by hepatocytes of substrates of these transporters. Ceftobiprole showed accumulation in OAT1- and OCT2-expressing cells suggesting that it may be a substrate of those transporters, both of which are present in the basolateral membrane of proximal tubular epithelial cells.³ However, an in vivo study using rats IV dosed with ceftobiprole or ceftobiprole medocaril showed no effect of co-administration of probenecid (an inhibitor of OAT1 and OAT3 that decreases renal tubular excretion of penicillin and other beta-lactam antibiotics) on the plasma time-concentration profiles for ceftobiprole. This suggests that renal excretion of ceftobiprole is not mediated by active transport processes.

New studies showed that ceftobiprole (0.5 to 200 μ M) produced neither direct nor time dependent inhibition of cytochrome P450 (CYP) isozyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) activity in human liver microsome preparations. Exposure of human hepatocytes to ceftobiprole medocaril at up to 200 μ M for three successive days produced no or a trivial increase in a similar panel of CYP enzyme activities. These results, plus the finding that ceftobiprole undergoes only limited metabolism by CYP enzymes, suggest that ceftobiprole is unlikely to show pharmacokinetic interactions with co-administered drugs that are CYP metabolised.

Toxicology

Acute toxicity

See Safety Pharmacology studies section above.

Repeat-dose toxicity

Studies using rats, dogs, and marmosets were reviewed in a previous evaluation. No new studies have been provided by the sponsor.

Relative exposure

Exposure ratios for two weeks of once or twice daily IV infusion of ceftobiprole medocaril, calculated on the basis of animal: human plasma AUCs at the no observable adverse effect level (NOAEL) were low: approximately 1 for rats and dogs and approximately between 2 and 4 for marmosets.

Major toxicities

The major target organ for ceftobiprole medocaril in rats and marmosets (but not dogs) was kidney. Drug precipitation was noted in proximal tubules, although it was not associated with damage. Precipitation in distal parts of the nephron was associated with local degeneration and necrosis. These changes were not observed in dogs, even at higher plasma and urine concentrations of ceftobiprole than produced changes in rats. Convulsions occurred in some rats and marmosets exposed to high test article concentrations (see also Safety pharmacology section). In some cases, the convulsions may have been associated with impaired renal function (that is, decreased drug clearance). Histaminergic reactions were noted in dogs but could be avoided by extension of the drug infusion time. Test article-related mortalities in rats and marmosets were associated with

² Roth M., Obaidat A. and Hagenbuch B. (2012) OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *British Journal of Pharmacology*, 165: 1260–1287.

³ International Transporter Consortium (2010) Membrane transporters in drug development. *Nature Reviews. Drug Discovery*. 9: 215–236.

renal toxicity and with vascular reactions (thrombo-embolism) at the infusion site. The sponsor's product information document states that renal disorders and hypersensitivity/anaphylactic shock are rare adverse reactions to ceftobiprole medocartil dosing in humans.

Genotoxicity

Previous results suggested that ceftobiprole medocartil could induce mutations and chromosomal aberrations in mammalian cells under in vitro conditions, although bacterial mutation and in vivo studies examining induction of chromosomal aberrations (mouse micronucleus assay) and unscheduled deoxyribonucleic acid (DNA) synthesis in rat hepatocytes showed no activity. A previous result from a bacterial mutagenicity assay and a new study using the in vitro Chinese hamster ovary (CHO)/Hypoxanthine-guanine phosphoribosyltransferase (HPRT) forward mutation assay both showed that ceftobiprole medocartil, produced using the sponsor's current synthesis process, lacked mutagenic activity in the presence or absence of metabolic activation. This suggests that current batches of ceftobiprole medocartil are not of genotoxic concern for patients.

Carcinogenicity

No carcinogenicity studies were submitted by the sponsor. This is acceptable given the relatively short period of patient treatment with ceftobiprole medocartil (maximum of 14 days) and the drug's limited activity in genotoxicity assays.⁴

Reproductive toxicity

No new studies for this area were presented. Previously analysed data for rats and Cynomolgus monkeys, in which exposure ratios of between 2 and 6 were achieved, suggested that ceftobiprole is neither a teratogen nor an inducer of fetal/maternal toxicity.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1⁵. This category is appropriate given the nonclinical data presented by the sponsor.

Local tolerance

Several new studies examined the tolerance of rabbits to intra-arterial, intramuscularly (IM), perivascular, or subcutaneous (SC) administration of ceftobiprole medocartil. No or slight irritation was seen in these studies.

Paediatric use

The sponsor has submitted new studies examining toxicity in juvenile rats receiving a daily SC dose of ceftobiprole medocartil. Exposure ratios at the NOAEL dose in these studies were low (<1; see table below). Similar to adults, possible targets for toxicity were kidney, liver and muscle (at site of injection).

Relative exposure

The following table summarises the relative exposure in rats as compared to humans.

Table 2: Relative exposure comparisons in rats versus humans

Species	Dosing period reference no.	Dose mg/kg/day ^a	AUC _{0-8h} µg·h/mL ^b	Exposure ratio ^c
Rat (SD)	PND1-PND25 (TOX8087)	37.5, 112.5, 225.0	63.2, 223, 573	0.2, 0.7, 1.9

⁴ International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Guideline S1a (1995): Guideline on the need for carcinogenicity studies of pharmaceuticals.

⁵ Pregnancy Category B1: Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Species	Dosing period reference no.	Dose mg/kg/day ^a	AUC _{0-8 h} µg·h/mL ^b	Exposure ratio ^c
	PND1–PND50 (TOX8611)	37.5, 75.0 , 187.5	77.6, 140.5 , 434.5	0.3, 0.5 , 1.4
Human	Clinical study no. 30982081-CSI-1004	[500 mg]	102 x 3	-

^a equivalent as ceftobiprole; ^b values for ceftobiprole on PND12 (TOX8087) and PND18 (TOX8611); ^c animal: human plasma AUC_{0-8 h}; Values at NOAEL are in boldface.

Note that the sponsor has requested that ceftobiprole medocaril be registered for the treatment of adult patients only.

Nonclinical summary

- Janssen-Cilag Pty Ltd had previously applied to register ceftobiprole medocaril sodium in Australia for the treatment of complicated skin and skin structure infections. That application was withdrawn in Australia, although the submitted nonclinical data were evaluated. The assessment and summary sections of the nonclinical report are based on both the previously evaluated data and the new nonclinical studies submitted with this application.
- The sponsor has submitted a high quality dossier of studies. The crucial genotoxicity, repeat-dose toxicity and reproductive and developmental toxicity studies were performed to GLP standard. The newly submitted studies provide useful information and cover deficiencies in the original presentation.
- The sponsor's primary pharmacology studies support the proposed indication for ceftobiprole medocaril sodium. No new studies were submitted.
- No new secondary pharmacodynamics or safety pharmacology studies were submitted. The major adverse findings from previously submitted studies were renal toxicity and convulsions.
- A new study showed that multiple hydrolytic enzymes, as well as non-enzymatic hydrolysis, contribute to the conversion of ceftobiprole medocaril to the active compound, ceftobiprole. Hence, pro-drug conversion is unlikely to be significantly affected by drug-drug interactions or by genetic polymorphisms that inactivate individual hydrolytic enzymes. Previously presented studies suggested that ceftobiprole is not extensively metabolised and is predominantly excreted in urine as the parental compound. Renal excretion of ceftobiprole is apparently not mediated by an active transport process in rats. New studies confirmed that exposure to the major plasma metabolite (derived by beta-lactam ring opening) is minor in both rats and dogs. New studies also demonstrated that ceftobiprole is neither an inhibitor nor inducer of major human CYP activities. Previous results showed that ceftobiprole is neither a substrate nor inhibitor of most drug transporters tested, although it is a modest inhibitor of the hepatocyte uptake transporters OATP1B1 and OATP1B3. Overall, it appears unlikely that there would be significant pharmacokinetic interaction between ceftobiprole and co-administered drugs.
- Previously evaluated repeat-dose toxicity studies showed that the major target organ for ceftobiprole medocaril in rats and marmosets but not dogs, was kidney. Renal toxicity was associated with precipitation of drug-like material in the distal tubules. Convulsions occurred in some rats and marmosets exposed to high test article concentrations. In some cases, the convulsions may have been associated with impaired renal function. Histaminergic reactions were noted in dogs. Test article-

related mortalities in rats and marmosets were associated with renal toxicity and with vascular reactions (thrombo-embolism) at the infusion site.

- Previous studies suggested that ceftobiprole medocartil could show mutagenicity/clastogenicity under in vitro but not in vivo conditions. New studies support the conclusion that ceftobiprole medocartil, produced using the sponsor's current synthesis process, lacks mutagenic activity in the presence or absence of metabolic activation. No carcinogenicity studies were performed. This is acceptable given the relatively short period of patient treatment with ceftobiprole medocartil (maximum of 14 days) and the drug's limited/lack of activity in genotoxicity assays.
- Previously analysed reproductive toxicity data for rats and Cynomolgus monkeys suggested that ceftobiprole is neither a teratogen nor inducer of fetal/maternal toxicity.
- Ceftobiprole medocartil drug product contains a large number of impurities. Although the sponsor has shown that current batches of ceftobiprole medocartil are not of genotoxic concern, many impurities have not been adequately qualified by repeat-dose toxicity studies⁶ and it is recommended that their levels be appropriately reduced or that toxicological studies that would allow qualification of higher impurity levels be performed.

Nonclinical conclusions and recommendation

- A number of minor deficiencies in the original submission, principally in the areas of metabolism, genotoxicity, local tolerance and impurities have now been addressed by the sponsor.
- The basic conclusions from the first assessment, regarding (but not limited to) primary pharmacology, genotoxicity and reproductive toxicity remain unchanged.
- The lack of effects of ceftobiprole medocartil in tests for teratogenicity and fetal/maternal toxicity support its placement in Pregnancy Category B1.
- Provided that concerns about the levels of impurities are addressed, there are no nonclinical objections to registration.
- Amendments to the draft Product Information were also recommended to the Delegate but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

⁶ The sponsor's estimates of qualified impurity levels derived from NOAELs and drug product impurity levels, from rat and marmoset repeat-dose toxicity studies, were scaled to body weight. The use of body weight rather than body surface area leads to improperly inflated estimates of qualified impurity levels. The TGA requested that the qualified impurity levels were calculated using body surface area and a more conservative value for human weight (that is, 50 kg rather than 70 kg). Such values are considerably lower than those presented by the sponsor

Introduction

Clinical rationale

In September 2009, the European Centre for Disease Prevention and Control and the EMEA issued a joint technical report entitled *The bacterial challenge: time to react*.⁷ This report focused on antibiotic-resistant bacteria and emphasised the urgency required to ensure adequate antibiotics are available to treat human disease due to these pathogens. The 7 important pathogens cited in the report were:

1. *S. aureus*, methicillin resistant (MRSA);
2. *S. aureus*, vancomycin intermediate resistant and vancomycin resistant (VISA/VRSA);
3. *Enterococcus* spp. (for example *Enterococcus faecium*), vancomycin resistant (VRE);
4. *Streptococcus pneumoniae*, penicillin resistance (PRSP);
5. Enterobacteriaceae (for example *E.coli*, *Klebsiella pneumoniae*), third generation cephalosporin resistant;
6. Enterobacteriaceae (for example *K. pneumoniae*), carbapenem resistant;
7. Non-fermentative gram-negative bacteria (for example *Pseudomonas aeruginosa*), carbapenem resistant.

Ceftobiprole has the potential to address some of the challenges brought about by the global pandemic of multi-drug resistant bacteria having demonstrated in vitro activity against:

- MRSA including prominent healthcare-associated and community-associated strains VISA/VRSA
- PRSP including *S. pneumoniae* isolates highly resistant to ceftriaxone and multi-drug resistant 19A *S. pneumoniae* clones

Ceftobiprole has demonstrated in vitro activity against daptomycin non susceptible, tigecycline resistant and linezolid resistant *S. aureus*. Ceftobiprole's potent activity against MRSA and PRSP extends the predominantly gram-negative spectrum of the well-established fourth generation cephalosporins (such as cefepime and ceftazidime), making it a 'fifth' generation cephalosporin.

Nosocomial pneumonia = pneumonia occurring > 48 hours after hospital admission which was not incubating at the time of admission.⁸ VAP = pneumonia which manifests after a patient has been on a ventilator for > 48 h. NP is one of the most common infectious diseases acquired in hospitals, affecting 0.5% to 1.7% of hospitalised patients^{9,10}, and accounting for approximately 25% of all intensive care unit (ICU) infections.¹¹ All-cause mortality for nosocomial pneumonia varies widely, ranging from 10% to 65% depending on patient population, clinical study setting treatment.¹² NP is caused by a wide spectrum of bacterial pathogens, including more resistant gram negatives, that is *P. aeruginosa*

⁷ ECDC/EMA Joint Technical Report. The bacterial challenge: time to react. 2009 EMEA/576176/2009.

⁸ Napolitano LM. Use of severity scoring and stratification factors in clinical trials of hospital-acquired and ventilator-associated pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S67-80.

⁹ Masterton R. The place of guidelines in hospital-acquired pneumonia. J Hosp Infect. 2007 Jun;66(2):116-22.

¹⁰ Lizioli A, Privitera G, Alliata E, et al. Prevalence of nosocomial infections in Italy: result from the Lombardy survey in 2000. J Hosp Infect. 2003 Jun;54(2):141-8.

¹¹ Torres A, Ferrer M, Badia JR. Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. Clin Infect Dis. 2010 Aug 1;51 Suppl 1:S48-53.

¹² Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S120-5.

(22%), *Klebsiella* sp. (10%), *Escherichia coli* (*E. coli*) (7%), *Acinetobacter* sp. (7%), and *Enterobacter* sp. (6.5%), and gram-positives such as *S. aureus* (28%), particularly MRSA.¹³ *S. aureus* has shown an increasing resistance to methicillin/oxacillin over the past four decades, with rates in Europe of 19.7% in 2009 as determined by the European Antimicrobial Resistance (EARS-Net) surveillance program of 198 laboratories in 22 countries.¹⁴ The rate of MRSA observed among ICU isolates of *S. aureus* is reported to be even higher at 34 to 44% in two large EU point prevalence studies.^{15,16} VAP represents a significant distinct clinical entity within NP related to patient factors including underlying disease and comorbidities.¹⁷

Community-acquired pneumonia=pneumonia acquired outside hospital or extended-care facilities or occurring \leq 48 h after hospital admission; annual incidence ranging from 3 to 40 per 1,000, and rates of hospitalisation of 40 to 60%; the rate at which patients with CAP are admitted to the ICU is approximately 10%.¹⁸ Mortality rate due to hospitalised CAP is 10%.¹⁸ This has not substantially decreased over the past decades partially because of the emergence of multidrug-resistant (MDR) pathogens, and an increased % of the population being at risk (for example, immunocompromised patients; advanced age). Current international treatment recommendations support a prompt initiation of 'appropriate' empiric antibiotics^{19,20} to avoid excess mortality and longer hospital stay.²¹ MRSA is an important cause of pneumonia, accounting for 20 to 40% of NP.²² The frequency of MRSA in CAP is still relatively low at <5% in most parts of the world but becoming more prevalent.²³

S. pneumoniae is the most frequent bacterial isolate in patients with CAP in the EU, that is, approximately 40 to 50% of all CAP in adults.²⁴ Drug resistance in *S. pneumoniae* occurs in \leq 20% of RTI²⁵, with an increase in invasive disease attributable to serotypes not covered

¹³ Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010 Aug 1;51 Suppl 1:S81–7.

¹⁴ Gagliotti C, Balode A, Baquero F, et al, the EARSNet Participants (Disease Specific Contact Points for AMR). *Escherichia coli* and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. *Euro Surveill*. 2011;16(11).

¹⁵ Lambert M, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis* 2011; 11: 30–38.

¹⁶ Vincent J, Rello J, Marshall J, et al. for the EPIC II Gp of Investigators. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. *JAMA*. 2009;302(21):2323–2329.

¹⁷ Sadfar N, Crnich CJ, Maki DG. The pathogenesis of ventilator-associated pneumonia: its relevance to developing effective strategies for prevention. *Respir Care* 2005; 50: 725–739.

¹⁸ Torres A, Rello J. Update in CAP and nosocomial pneumonia. *Am J Respir Crit Care Med* 2010, vol. 181 no. 8: 782–787.

¹⁹ Torres A, Ewig S, Lode H, Carlet J; European HAP working gp. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med*. 2009;35(1):9–29.

²⁰ BTS: Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009 Oct;64 Suppl 3:iii1–55. PubMed PMID: 19783532.

²¹ Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 115:462–474.

²² Rubinstein E, Kollef MH, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2008 Jun 1;46 Suppl 5:S378–85.

²³ Randolph A, Vaughn F, Sullivan R, et al. Critically ill children during the 2009–2010 influenza pandemic in the United States. *Pediatrics*, published online 7 November 2011, doi: 10.1542/peds.2011–0774.

²⁴ Höffken G, Lorenz J, Kern W, et al. Epidemiology, diagnosis, antimicrobial therapy and management of community-acquired pneumonia and lower respiratory tract infections in adults. Guidelines of the Paul-Ehrlich-Society for Chemotherapy, the German Respiratory Society, the German Society for Infectiology and the Competence Network CAPNETZ Germany. *Pneumologie*. 2009 Oct;63(10):E1–68.

²⁵ Richter SS, Heilmann KP, Dohrn CL, et al. Changing epidemiology of antimicrobial-resistant *Streptococcus pneumoniae* in the United States, 2004–2005. *Clin Infect Dis* 2009 Feb 1;48(3):e23–33.

by the current pneumococcal vaccines, for example serotype 19A.^{26,27} The reported EU prevalence of *S. pneumoniae* isolates submitted to the EARS-NET surveillance network in 2010 with 3.7% penicillin resistance; 9.3% intermediate penicillin resistance; macrolide resistance among these isolates was 15%.²⁸ Other important bacterial causes of CAP include *H. influenzae*, *S. aureus*, and gram-negative enteric organisms. *S. aureus* including MRSA has emerged as an important pathogen in severe necrotising CAP, with a mortality rate of up to 56%.²⁹ According to reports from the US Centers for Disease Control and Prevention (CDC), the number of severe CAP-MRSA cases continues to rise, with a peak incidence during the annual influenza season.^{30,31} High mortality rates due to community-acquired MRSA (CA-MRSA) have also been reported in Europe.³² Secondary bacterial pneumonia is a common cause of death in patients with seasonal influenza, with co-infections found in approximately 25% of flu-related deaths.^{33,34} In a US urban study, MRSA found in 2.4% (14/595) of all cultures, and 14% of positive bacterial cultures, in CAP patients admitted to hospital during 2 consecutive flu seasons.³⁵

Australia: Lower respiratory tract infections (LRTI) account for approximately 3 million visits to General Practitioners (GPs) each year.³⁶ The combined death rate for pneumonia and influenza positions these respiratory infections as the sixth leading cause of death. In 2002, pneumonia and influenza accounted for 3084 deaths (2.34% of all deaths in Australia) and 43,953 hospital admissions (average stay=6.3 days). Each year, CAP is associated with an overall mortality rate of 11.8% for hospitalised patients aged >65 years. This mortality rate increases to 19.2% if ≥2 co-morbidities are present. The direct/indirect cost burden of CAP is >A\$500million/year. This Case Statement also includes information about increasing antibiotic resistance in Australia and the need for new antibiotics to treat pathogens, namely *S.pneumoniae*, MDR *S.aureus* and MDR gram-negative pathogens. Importantly, while CAP and NP are of public health concern, there is a lack of epidemiological studies examining the incidence in Australia (Murdoch 2014).³⁷

²⁶ Tarragó D, Aguilar L, García R, et al. Evolution of clonal and susceptibility profiles of serotype 19A *Streptococcus pneumoniae* among invasive isolates from children in Spain, 1990 to 2008. *Antimicrob Agents Chemother.* 2011 May;55(5):2297–302.

²⁷ Beall BW, Gertz RE, Hulkower RL, et al. Shifting genetic structure of invasive serotype 19A pneumococci in the United States. *J Infect Dis.* 2011 May 15;203(10):1360–8.

²⁸ European Antimicrobial Resistance Surveillance Network (EARS-Net) interactive database. <<http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx>. Accessed 8 March 2012.

²⁹ Gillet Y, Vanhems P, Lina G, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *CID* 2007;45:315–321.

³⁰ Centers for Disease Control. Mortality and Morbidity Weekly Report. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza – Louisiana and Georgia, December 2006–January 2007. 2007 Apr 13;56(14):325–329.

³¹ Centers for Disease Control. Mortality and Morbidity Weekly Report. Bacterial Coinfections in Lung Tissue Specimens from Fatal Cases of 2009 Pandemic Influenza A (H1N1) – United States, May–August 2009. 2009;58(38):1071–1074.

³² Dufour P, Gillet Y, Bes M, et al. Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections in France: Emergence of a Single Clone That Produces Panton-Valentine Leukocidin. *Clinical Infectious Diseases* 2002; 35:819–24.

³³ Simonsen L. The global impact of influenza on morbidity and mortality. *Vaccine.* 1999;17(Suppl 1):S3–10.

³⁴ Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med.* 2005;353:2559–67.

³⁵ Moran GJ, Krishnadasan A, Gorwitz RJ et al. Prevalence of Methicillin-Resistant *Staphylococcus aureus* as an Etiology of Community-Acquired Pneumonia. *Clinical Infectious Diseases* 2012;54(8):1126–33.

³⁶ The Australian Lung Foundation, 'Respiratory Infectious Disease Burden in Australia', Edition 1, March 2007

³⁷ Murdoch KM, Mitra B, Lambert S, Erbas B. *Australas Emerg Nurs J.* 2014 What is the seasonal distribution of community acquired pneumonia over time? A systematic review. Feb;17(1):30-42. doi: 10.1016/j.aenj.2013.12.002. Epub 2014 Jan 15.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 21 clinical pharmacology studies, including 14 that provided pharmacokinetic (PK) data and 7 that provided pharmacodynamic (PD) (and PK/PD) data.
 - 1 population PK analyses in 3 parts: population PK analysis, PK/PD analysis, and target attainment rate calculations.
 - 2 Phase III pivotal efficacy/safety studies.
 - 4 other efficacy/safety studies/reports including those conducted in cSSTI.

Paediatric data

The submission contained paediatric data from one PK study, 30982081-CSI-1006.

Good clinical practice (GCP)

The clinical studies in this Application complied with CPMP/ICH/135/95 an internationally accepted standard for the design, conduct, recording and reporting of clinical trials, however the cSSTI studies have major GCP deficiencies.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic.

Table 3: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	NP16104, BAP0006, BAP00210	* *
	- Multi-dose	BAP00010, BAP00058 BAP00393 JNS015-JPN-01	* * *
PK in special populations	Target population § - Single dose		
	- Multi-dose		
	Hepatic impairment	not done	
	Renal impairment	BAP00018 30982081-CSI-1007 CEFTO-NOS-1001	*
	Obese adults	CEFTO-CSI-1008	*

PK topic	Subtopic	Study ID	*
	Neonates/infants/children/adolescents	30982081-CSI-1006	*
	Elderly	not done	
Genetic/gender-related PK	Males versus females	BAP00036 30982081-CSI-1004	*
PK interactions		not done	
Population PK analyses	Healthy subjects	Completed JNJ-30982081	*
	Target population	Patients with cSSSI JNJ-30982081	*

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Note: the ** studies above also included PD data which is presented below.

Evaluator's conclusions on pharmacokinetics

The applicant has provided a comprehensive PK program (in adults) and a justification for the lack of drug-drug interaction studies. This reveals linear and time-independent PK and a drug that is excreted predominantly unchanged in urine. The programme of studies in renally impaired individuals supports the proposed dosing in those with mild to moderate and severe renal impairment (including dialysis subjects).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

Table 4: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	BAL penetration	30982081-CSI-1005	*
		30982081-CSI-1002	*
	Tissue penetration in adipose and skeletal tissue	CEFTOPED-1001	*
	Penetration into bone	CEFTONOS-1002	*
	Penetration into epithelial lining and alveolar macrophages in the lung**		*
Secondary Pharmacology	Effect on intestinal flora	CEFTO-BAC-1002	*
	Effect on QTc interval	30982081-CSI-1001	*

PD Topic	Subtopic	Study ID	*
		30982081-CSI-1003	*
Population PD and PK-PD analyses	Healthy subjects	-	
	Target population	-	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

None of the PD studies had deficiencies that excluded their results from consideration aside from Study CEFTONOS-1002 which was terminated early due to very poor enrolment before study drug given.

Evaluator's conclusions on pharmacodynamics

Ceftobiprole is a fifth generation cephalosporin with potent activity in nonclinical models against the most common pathogens causing CAP and many of those causing NP. Uniquely, it combines the broad gram negative activity of fourth generation cephalosporin, with activity against *Staph aureus* incl. MRSA. The drug appears to be bactericidal and this may be an advantage in some situations, and has high penetration into tissues of relevance that is, the lung. It appears well tolerated. Its broad spectrum of activity means it can be given as monotherapy. The secondary impact on faecal flora and selection for organisms such as *C.difficile*, have been studied but only in the short term and faecal samples were not collected routinely in the pneumonia studies. The drug has a straightforward PK profile and aside from reduced dosing in renal impairment, there is low risk of drug-drug interactions; again this makes it appealing in the clinical setting.

Dosage selection for the pivotal studies

Animal models demonstrate the time the concentration of an antibiotic remains above the Minimum Inhibitory Concentration (MIC) ($T > MIC$) is the PK/PD driver for ceftobiprole efficacy. For coverage including gram-negative pathogens the magnitude of $\%T > MIC$ should be $\geq 50\%$. Using population PK approaches, projected and estimated probability of target attainment demonstrate the adequacy of the 500 mg three times a day (tds) 2 h infusion dosing for broad spectrum coverage in NP. As per Efficacy (see below), observed PK/PD targets and parameters from these models were predictive of microbiological and clinical response in BAP248/307.

Efficacy

Studies providing efficacy data

Only the efficacy studies that pertain to the proposed indications (NP and CAP) are included. The cSSTI studies, BAP00034; BAP00154; BAP00414 were not evaluated because of GCP concerns. Safety data arising from these studies is reviewed below under *Safety*. Study 30982081, in neutropaenic patients was terminated early for administrative reasons.

Evaluator's conclusions on efficacy of Zevtera for NP and CAP

The design of both studies was in accordance with the European Medicines Agency (EMA) guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. The double-blind design adds substantially to the strength of the findings. The

reason for this being so important is that 'clinical response' in many infectious diseases including bacterial pneumonia can be rather subjective even with clear guidance in the protocol. The double-blind design removes much of the bias. All bacterial pneumonia studies are additionally hampered by the poor yield of organisms that are causative, which is why 'clinical cure' is used as a primary determinant of efficacy. Both studies demonstrate the efficacy of ceftobiprole – with caveats - and as reviewed in greater detail in *Safety*, show ceftobiprole to be reasonably well tolerated and safe in the treatment of nosocomial pneumonia and CAP requiring hospitalisation. Both studies met their primary objective of demonstrating the non-inferiority of ceftobiprole, to an adequately-dosed 'standard-of-care' active comparator. But, there are two important issues. First, in the NP Study BAP248/307, the choice of comparator Arm, whilst making good sense, is probably still not standard-of-care in most centres, let alone at the time this study was being conducted in 2005-2007. In the design, assumptions had to be made about the expected clinical cure rates of the comparator arm, as ceftazidime and linezolid had never been partnered together (at least not then) in a clinical trial. While there is robust evidence that ceftobiprole is as efficacious as ceftazidime+linezolid as measured by clinical cure rates, pneumonia-specific mortality, and all-cause mortality in nosocomial pneumonia, this is only true if the VAP subjects are excluded.

While BAP248/307 only enrolled a relatively small subset of VAP subjects (210 out of 781 (27%) subjects with NP), clinical cure and microbiological eradication rates at the Test-Of-Cure (TOC) visit were lower and all-cause mortality numerically higher, in the ceftobiprole gp than in the linezolid/ceftazidime gp, although none of these differences were statistically significant. It is not completely clear to the evaluator that the baseline (co-morbidities, severity of disease) and on-study differences completely explain this finding, even with the post hoc analysis. However, in such a heterogenous group with numerous confounding factors and relatively small numbers, it is difficult to draw conclusions. An in depth PK/PD analysis (which included an analysis of %T>MIC for individual patients considering MICs from isolated pathogens) showed no apparent difference in exposure or target attainment between ceftobiprole and linezolid+ceftazidime treated VAP subjects. The sponsor concludes that this means that inadequate exposure of VAP subjects to ceftobiprole is not an explanation for the observed difference in clinical or microbiological outcome between treatment groups. The clinical evaluator is now sure whether to completely agree with this, organism(s) identified as the 'likely' organism(s) may not have been the main players, this is often the case for example with pseudomonas, which may be a 'passenger' and not a 'pathogen'. It is just possible, that ceftazidime plus linezolid outperformed ceftobiprole in the VAP setting for reasons as yet to be determined. The US FDA has recently amended its regulatory guidelines for hospital-acquired pneumonia and VAP such that separate studies are conducted for VAP. This amendment recognises the heterogeneity within the study population and the ways to try and overcome these through stratification by Acute Physiology and Chronic Health Evaluation II (APACHE II) score and time of onset of VAP after onset of mechanical ventilation.

One of the rationales for the development of this fifth generation cephalosporin is for MDR organisms. So how well did the drug perform from the microbiological perspective? In CAP-3001, there were similar microbiological, clinical cure and microbiological eradication rates between treatment groups for gram-positive and gram-negative pathogens. With regard to the NP (excluding VAP) population, similar clinical cure rates and microbiological eradication rates were observed for gram-positive pathogens including MSSA and MRSA. For gram-negative pathogens overall, clinical cure rates were 70% (51/73) and 78% (62/80) in the ceftobiprole and linezolid/ceftazidime groups, respectively; microbiological eradication rates were 59% (43/73) in the ceftobiprole group and 70% (56/80) in the linezolid+ceftazidime group. These small difference seems to have been partially driven by an imbalance in *Haemophilus* species (2/5 in the ceftobiprole group versus 8/9 subjects with microbiological eradication in the

linezolid+ceftazidime group). This finding does not seem consistent with the known in vitro activity of ceftobiprole against *Haemophilus* species and is likely a chance finding. In the NP (excluding VAP) population, another less pronounced imbalance in microbiological eradication rates was for *A. baumannii* (4/8 subjects in the ceftobiprole group versus 9/12 subjects with microbiological eradication in the linezolid+ ceftazidime group). Subjects with Acinetobacter infections in CAP and VAP had similar microbiological eradication with ceftobiprole. However, numbers are very small and these data should not be overcalled. Microbiological eradication rates in the nosocomial pneumonia (excluding VAP) subgroup were comparable between treatment groups for other gram negative organisms.

The results of Study CAP-3001 demonstrate that ceftobiprole is as effective as a high dose of 2 g ceftriaxone once a day (qd) ± linezolid in treating subjects hospitalised with CAP. The most prevalent pathogen identified in the study was *S. pneumoniae* but importantly it was only found in 28 subjects, that is, a very small number overall. While cure rates were very high, the issue is that culture positive bacterial pneumonia occurs in the minority using traditional techniques, sequencing in blood may overcome some of these issues in future trials if such results can be provided real-time. Clinical cures for other important CAP pathogens in the ceftobiprole gp included 7 (100%) *Staph.aureus*; 6 (100%) with *E. coli*, 4 (80%) with *K. pneumoniae*, 1 (100%) with *K. oxytoca*, 4 (100%) with *M. catarrhalis*.

Ceftobiprole constituted a unique new cephalosporin and is a welcome addition to the antibiotic armamentarium providing a new option to treat current/emerging pneumonia infections due to more resistant bacteria. In addition, it appears to have a favourable toxicity profile, at least with short exposures, although tds IV dosing is a major disadvantage in clinical practice.

Safety

Studies providing safety data

There were no studies that assessed safety as a primary outcome. The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, BAP248/307 and 30982081-CAP-3001, the following safety data were collected:

- General adverse events (AEs): assessed and graded by study investigators against standard toxicity tables. Coded using MedDRA³⁸. A treatment emergent AE (TEAE) is an AE that first occurred, or worsened in severity, at or after the date and time of the start of administration of the first dose of IV study drug. The numbers and % of subjects with specific TEAE was summarised by system organ class (SOC) and preferred term (PT) for each treatment/dose and analysed for the following subcategories: treatment related AEs (TRAEs), serious AEs (SAEs), treatment-related serious AEs and AEs resulting in treatment discontinuation. AE tabulated by severity and relationship to the study medication for each treatment/dose.
- AEs of particular interest that is, gastrointestinal (GI), hypersensitivity (for example rash), were assessed as above.
- Vital Signs, Physical Examination and electrocardiogram (ECG);

³⁸ The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices.

- Laboratory tests, including full blood count (FBC) and differential; renal function, liver function tests (LFTs) and electrolytes, performed at study visits as detailed in the protocol. Graded and assessed as above.

Dose-response and non-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data. For each of these Phase I studies, there is a summary section on safety.

Patient exposure

There are 25 completed clinical studies, with 539 subjects in 20 Phase I studies, 40 cSSTI subjects in the Phase II Study BAP00034, 632 CAP subjects in CAP-3001, 772 subjects with NP in BAP248/307 and 1,593 cSSTI subjects in 2 Phase III studies BAP00154 and BAP00414. Safety data from CAP-3001 and BAP248/307 were analysed both by study and in an integrated overall safety analysis. Safety data from the 2 cSSTI Phase III and single cSSTI Phase II studies were integrated for analysis and compared with the pooled analysis of safety data from the 2 Phase III pneumonia studies (=safety analysis sets). See Tables 5 and 6.

Table 5: Phase II and III efficacy and safety studies

Study	Design and dosage	Number of subjects / Treatment
Phase 2 Efficacy and safety study		
BAP00034	Open-label, multicenter study of ceftobiprole in subjects with complicated skin and skin structure infections A 30- or 60-minute i.v. infusion of 750 mg ceftobiprole twice daily for 7 to 14 days	N=40
Phase 3 Efficacy and safety studies		
CAP-3001	Randomized (1:1), double-blind, multicenter study of ceftobiprole versus ceftriaxone with or without linezolid in the treatment of CAP requiring hospitalization. Subjects received a 2-hour i.v. infusion (3 times daily) of 500 mg ceftobiprole or 2000 mg ceftriaxone (once daily) with or without 600 mg linezolid (twice daily). The duration of treatment was 5 to 14 days with an option to switch to oral therapy (cefuroxime axetil, 500 mg, twice daily) after a minimum of 3 days of i.v. treatment with study medication based on the specific clinical criteria as outlined in the protocol.	N=632* ceftobiprole, n=310 ceftriaxone with or without linezolid, n=322
BAP248/307	Randomized (1:1), double-blind, multicenter study of ceftobiprole versus linezolid plus ceftazidime in the treatment of nosocomial pneumonia, including subjects with VAP. Subjects received a 2-hour i.v. infusion (3 times daily) of 500 mg ceftobiprole or 600 mg linezolid (twice daily) plus 2000 mg ceftazidime (3 times daily) for 7 to 14 days.	N=772* ceftobiprole, n=386 linezolid plus ceftazidime, n=386
BAP00154	Randomized (1:1), double-blind, multicenter study of ceftobiprole versus vancomycin in the treatment of complicated skin and skin structure infections A 1-hour i.v. infusion (twice daily) of 500 mg ceftobiprole or 1,000 mg vancomycin for 7 to 14 days, with a possible extension up to 28 days	N=771* ceftobiprole, n=389 vancomycin, n=382
BAP00414	Randomized (2:1), double-blind, multicenter study of ceftobiprole versus vancomycin plus ceftazidime in the treatment of complicated skin and skin structure infections A 2-hour i.v. infusion of 500 mg ceftobiprole (t.i.d)/1-hour i.v. infusion of placebo (twice daily) or a 1-hour i.v. infusion of 1,000 mg vancomycin (twice daily)/2-hour i.v. infusion of 1,000 mg ceftazidime (3 times daily) for 7 to 14 days, with a possible extension up to 28 days	N=822* ceftobiprole, n=543 vancomycin plus ceftazidime, n=279

* Number of subjects in the Safety analysis set.

Table 6: Extent of Exposure - Ceftobiprole in the Safety analysis sets

	Ceftobiprole			
	CAP	NP	Pooled Pneumonia	Pooled cSSTI
	CAP-3001	BAP00248/307	Studies	Studies
	(N=310)	(N=386)	(N=696)	(N=972)
Duration (days)				
N	310	386	696	972
Category, n(%)				
< 5	135 (43.5%)	69 (17.9%)	204 (29.3%)	72 (7.4%)
5 - 7	118 (38.1%)	172 (44.6%)	290 (41.7%)	603 (62.0%)
8 - 10	50 (16.1%)	80 (20.7%)	130 (18.7%)	130 (13.4%)
11 - 14	7 (2.3%)	61 (15.8%)	68 (9.8%)	140 (14.4%)
15 - 21	0	4 (1.0%)	4 (0.6%)	27 (2.8%)
22 - 28	0	0	0	0
Mean (SD)	5.52 (2.610)	7.60 (3.427)	6.68 (3.256)	8.06 (3.198)
Median	5.00	7.00	7.00	7.00
Range	(0.3; 14.3)	(0.3; 18.0)	(0.3; 18.0)	(0.3; 21.0)

Safety issues with the potential for major regulatory impact

No such issues were revealed.

Post marketing data

This is an evaluation of a new chemical entity and therefore no postmarketing data are available.

Evaluator's conclusions on safety

In the pooled Phase III pneumonia studies, 29.7% of all ceftobiprole treated subjects and 25.6% of all comparator-treated subjects experienced ≥ 1 one drug-related AE. Most commonly (in $\geq 1\%$ of those treated with ceftobiprole): nausea (4.3% of subjects), diarrhoea (4.2%), vomiting (3.3%), hyponatraemia (2.7%), phlebitis (2.3%), dysgeusia (1.6%), headache (1.4%), rash (1.1%), alanine aminotransferase (ALT) increased (1.1%) and aspartate aminotransferase (AST) increased (1.0%). The safety of ceftobiprole was also evaluated in special populations, by age, gender, race, renal impairment and hepatic impairment. Analysis of these special populations revealed no particular safety signal of concern especially in the NP study, where patients were generally much sicker. The clinical program did not reveal any worrisome signal in regards to the selection of resistance but relatively few patients have been exposed over only a short period of time. Broad spectrum cephalosporins are recognised to increase the risk of *C. difficile* colonisation and colitis; it would be expected that Zevetra would be no different in this regard.

What is the real risk to health of Australians with the registration of this fifth generation cephalosporin?

Overall the clinical evaluator thinks the risk is low, the rationale for this is:

1. It is clearly quite difficult for *Staphylococcal* and *Streptococcal* species to develop resistance and even very resistant species remain susceptible to the drug;

2. Mechanisms of resistance to various gram negatives have been defined, some of these highly resistant strains are already resistant to the drug so ceftobiprole is unlikely to make the situation worse;
3. The sponsor has projected the expected use of ceftobiprole in Australia. Use in 2016 is expected to be in 50 patients rising to 2650 in 2020, average number of days of dosing will be 8 (extrapolated from the Phase III pneumonia studies). In other words, there will be very restricted use of the drug (small numbers, short exposure) and this means the risk of dissemination of ceftobiprole resistant strains, should they occur, is low;
4. The clinical development program confirms using the recommended dose of 500 mg tds as a 2 h IV infusion has extremely high coverage of the target pathogens isolated during the 2008 surveillance study.

In summary, although the risk of emergence of ceftobiprole resistance appears low for gram positive organisms (pneumonia-causing pathogens), the risk is likely greater for some of the gram negative organisms. Importantly, ceftobiprole resistance may occur for reasons not directly related to the use of the drug in Australia for example global movement of very resistant pathogens as people and even populations travel and hence, ongoing *international* pharmacovigilance and microbiological surveillance activities are essential. In Australia, the incidence of resistance in CAP organisms is growing but it still remains relatively low. The clinical evaluator's greatest concern is that when Zevtera is approved for use in CAP, the drug will be used empirically and *not stopped* even when the organism is revealed to be sensitive to narrower spectrum agents. The use of a very broad-spectrum antibiotic for a common condition such as CAP which is frequently caused by sensitive bacteria, for example penicillin sensitive pneumococci when the global push is to use narrower spectrum antibiotics wherever possible, seems counter-intuitive. If the drug is misused on a global scale, then there is a risk of the selection of increasingly resistant organisms.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Zevtera in the proposed usage are:

- A broad-spectrum antibiotic that combines potent gram positive (including for MRSA) and gram negative activity against the common pneumonia-causing bacteria; the evaluator can see the particular utility of this drug for nosocomial infections and perhaps for CAP in a patient with a particular risk for more-resistant organisms (past/current history; other comorbidities; co-infection with respiratory tract viruses that might increase risk of invasive *Staphylococcal* infection including MRSA);
- Favourable PK profile with linear PK and no accumulation seen; dose adjustments for varying degrees of renal impairment appear supported by the data derived from the PK program;
- Little potential for drug-drug interactions, this is important as the target population are more likely to be elderly with other comorbidities and using polypharmacy as a consequence;
- Rapid mode of action;
- Can be given as monotherapy which avoids the use of two (or more) different antibiotics to provide 'appropriate' antibiotic coverage in those very ill with bacterial pneumonia;

- Alternative agents such as linezolid, while an excellent gram positive antibiotic, have idiosyncratic haematological and neurological AEs. To date no such idiosyncratic reactions have been revealed for this drug but patient exposure is limited. Other broad-spectrum penicillins (such as Timentin[®]) are well tolerated but do not have MRSA activity in which case they are often combined with glycopeptides or linezolid if MRSA is suspected.

First round assessment of risks

The risks of Zevtera in the proposed usage are:

- While multidrug resistant organisms are of growing concern worldwide, they are not of such a great concern, yet, in Australia at least not for CAP. The problem with empirical use of such a broad spectrum antibiotic is that it will inevitably be used for sensitive organisms that simply don't need such a broad-spectrum antibiotic for treatment. Although the development of resistance to the drug especially for gram positives is low, there still is a potential risk for the selection of resistant organisms and/or overgrowth with *C. difficile* and subsequent colitis;
- The drug is associated with quite a number of GI toxicities especially nausea and altered taste, while tolerated reasonably well in the clinical trials, these toxicities may be more problematic in the 'real-life' setting;
- The drug has to be given IV as a 2 h infusion tds and this is not very user friendly;
- The potential for the drug to interfere with some forms of testing for creatinine may be an issue, depending on how widespread those platforms are utilised in biochemistry laboratories. This may be an issue in those with renal impairment for whom dose adjustment is required;
- There is no oral treatment equivalent at this juncture for step-down. The clinical evaluator notes the step-down option in the CAP study was a first generation cephalosporin, one could argue that most of the patients enrolled in the CAP-3001 study would have done just as well on a first generation cephalosporin from the onset.

First round assessment of benefit-risk balance

The benefit-risk balance of Zevetra, given the proposed usage, is favourable.

First round recommendation regarding authorisation

The clinical evaluator recommended approval of the drug for nosocomial (hospital-acquired) bacterial pneumonia (excluding ventilator-associated pneumonia) and community acquired bacterial pneumonia requiring hospitalisation.

Clinical questions

Pharmacokinetics

1. Renal function tests are usually supplied as an estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; what is the risk in terms of incorrect dosing if the Cockcroft-Gault formula is not used to calculate creatinine clearance?

Pharmacodynamics

No questions.

Efficacy

1. Unclear to what extent MRSA and NORSA and resistant *S.pneumoniae* are a causative agent in CAP in Australia? In which case do you really need to cover these organisms empirically when treating CAP?
2. Does the sponsor have any concerns about the use of the drug for *Haemophilus* sp., there seemed to be a signal, albeit small, that the drug did not perform so well in a couple of patients?
3. How will the sponsor monitor the 'off-label' use in VAP which is very likely to happen, especially as definitions of VAP can be quite confusing?

Safety

No questions.

Second round evaluation of clinical data submitted in response to questions

No second round clinical evaluation was conducted. The sponsor's response to the clinical questions was taken into account when the delegate prepared the Overview (*Overall conclusion and risk/benefit assessment below*).

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan (EU-RMP version 2.0 dated 11 June 2014 (data lock point 19 April 2014), Australian Specific Annex version to the EU-RMP) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of Ongoing safety concerns which are shown at Table 7.

Table 7: Summary of Ongoing safety concerns.

Important identified risks	Hepatic enzyme elevations. Hyponatraemia. Anaphylaxis. Hypersensitivity reactions Pseudomembranous colitis / <i>Clostridium difficile</i> colitis. Injection/ infusion site reactions. Localised fungal infections (including vulvovaginal, oral and cutaneous fungal infections). Renal toxicity, including potential interactions with nephrotoxic drugs. Convulsions. Precipitation of infusion solutions when mixed with calcium-containing solutions.
Important potential risks	Development of drug-resistant bacteria. Off label use in children and adults. Haemolytic anaemia / Coombs test. Interaction with copper reduction technique to measure urine glucose. Interaction with Jaffé method to measure creatinine. Interaction with drugs transported via OATP1B1 and OATP1B3. CYP drug interactions.
Important missing information	Pregnancy and lactation. Paediatric subjects. Use in patients with hepatic impairment. Use in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression. Safety data in patients with end stage renal failure.

Pharmacovigilance plan

Routine pharmacovigilance have been proposed to monitor all the safety concerns. This includes targeted follow-up questionnaires for 'renal toxicity', 'development of drug-resistant bacteria', 'off-label use in children and adults', 'haemolytic anaemia/positive Coombs test', 'interaction with copper reduction technique to measure urine glucose' and 'interaction with Jaffé method to measure creatinine'. In addition, future clinical studies will include Coombs testing, haptoglobin and reticulocyte testing to monitor 'haemolytic anaemia'. Monitoring of ceftobiprole's activity against clinically relevant pathogens through in vitro surveillance studies of clinical isolates will be conducted at geographically distributed sites including multiple sites in various European countries. A post-authorisation safety study (PASS) BPR-PAS-001 has been planned to gather evidence on the use of ceftobiprole in patients with impaired hepatic or renal function, and HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities through the Australian PI and Consumer Medicine Information (CMI) for all the safety concerns identified in the RMP. No additional risk minimisation has been proposed.

The sponsor also advised in the ASA that there is no difference between the EU and Australian risk minimisation activities.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluator's evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>1. Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>The applicant confirms that there are no additional safety considerations other than those already identified in the Risk Management Plan.</i></p>	<p>The sponsor should provide response to the clinical evaluator's comments in the first round CER.</p>
<p>2. The sponsor should provide the date and version number for the ASA document.</p>	<p><i>The date of the ASA document is 24 October 2014; the version is 1.0.</i></p>	<p>The sponsor's response is satisfactory.</p>
<p>3. The annexes to the EU-RMP do not appear to be included in the submission. They are part of the EU-RMP and the sponsor should provide the content of the annexes. In addition, it is unclear whether the study protocol for PASS BPR-PAS-001 and the targeted follow-up questionnaires are part of the annexes. These should also be provided to the TGA for review.</p>	<p><i>The annexes to the EU-RMP were sent to the TGA as an attachment to the response to the matter raised in the Notification Letter dated 28 November 2014.</i></p> <p><i>The PASS protocol (BPR-PAS-001) is included in Annex 5. The targeted questionnaires to monitor the safety concerns identified in the RMP are included in Annex 7.</i></p> <p><i>The EU-RMP including all of the annexes has been included in the submission.</i></p>	<p>The sponsor's response is satisfactory. The evaluator has noted the complete version of the EU-RMP.</p>
<p>4. The following adverse events have been related to the use of other antibiotics in the cephalosporin class. The sponsor should provide justification to why they are not relevant to ceftobiprole. Otherwise, they should be added to the list of safety concerns in the ASA:</p> <ul style="list-style-type: none"> Serum sickness-like syndrome; Toxic epidermal necrolysis; Steven-Johnson syndrome. 	<p><i>For ceftobiprole, there were no reports of treatment-emergent adverse events of serum sickness syndrome, serum sickness like reaction, toxic epidermal necrolysis, or Stevens-Johnson syndrome in the Phase III pneumonia studies or the Phase I studies.</i></p> <p><i>Taking into account the proposed indications (treatment in adults of hospital-acquired pneumonia [HAP], excluding ventilator-associated pneumonia [VAP], and of community-acquired pneumonia [CAP]), the applicant has identified the following cephalosporins as relevant</i></p>	<p>The sponsor's justification is acceptable in the regulatory context. The sponsor should undertake to monitor and report the occurrence of these adverse events in the Periodic Safety Update Reports.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p><i>comparators to ceftobiprole: ceftazidime, ceftriaxone, and cefepime. Table 9 presents the information available for these drugs in regard to the adverse events referred to, from European Summary of Product Characteristics (SmPCs), Australian PIs and publicly available Risk Management Plans.</i></p> <p>[RMP evaluator: table not included]</p> <p><i>Summary</i></p> <p><i>There were no reports of the adverse events referred to in the question in any of the ceftobiprole clinical studies. Serum sickness was not identified as an adverse drug reaction for the selected cephalosporins, and Stevens-Johnson syndrome and toxic epidermal necrolysis have only been reported very rarely or with unknown frequency during postmarketing experience with these drugs. Nor have any of these events been identified as an important identified or potential risk in any available Risk Management Plan for these drugs.</i></p> <p><i>The applicant therefore does not propose to add serum sickness-like syndrome, toxic epidermal necrolysis, or Stevens-Johnson syndrome to the list of safety concerns in the ASA.</i></p>	
<p>5. The sponsor should clarify the frequency of hypokalaemia. The proposed Australian PI shows 7.3% of patients had hypokalaemia in clinical studies. However, according to the approved SmPC (http://www.medicines.org.uk/emc/medicine/29764), it is an uncommon event occurring in less than 1% of patients.</p>	<p><i>The distinction between the two rates is that the frequency of hypokalaemia in the Australian PI (7.3%) refers to adverse events, while the frequency of hypokalaemia in the UK SmPC refers to adverse drug reactions.</i></p> <p><i>The figure for proposed Australian PI reflects reports of adverse events with the MedDRA Preferred Term 'hypokalaemia' in pooled pneumonia studies (51/696, 7.3%). In the approved UK SmPC, hypokalaemia is included as an uncommon adverse reaction (6/696, 0.9%).</i></p>	<p>The sponsor's response is acceptable.</p>
<p>6. It should be noted that the pattern of antibiotic activity and resistance in Australia and the EU can be different. The</p>	<p><i>The applicant intends to set up annual surveillance programmes on S. aureus and Enterobacteriaceae for ceftobiprole in collaboration with the</i></p>	<p>The sponsor's response is satisfactory.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>sponsor should include at least six Australian sites in the monitoring system to ensure the surveillance studies of clinical isolates adequately reflect the local situation. Representation should include isolates from different Australian institutions rather than many isolates from few sites. It should be noted that this is in line with the pharmacovigilance activities required for other antibiotics in the previous RMP evaluations.</p>	<p><i>Australian Group on Antimicrobial Resistance, once the commercial sponsor for Zevtera in Australia has been defined, and local pharmacovigilance activities have been established (see the Australian-specific Annex to the EU-RMP, Section 2.1). The surveillance program will be set up as advised by the TGA (that is, inclusion of at least six Australian sites in the monitoring system, inclusion of isolates from different Australian institutions).</i></p>	

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed all of the issues identified in the RMP evaluation report.

There are additional recommendations (see below).

Outstanding issues

Additional recommendations by the Advisory Committee on Safety of Medicines (ACSOM)

Recommendation 1: Potential fluid overload is identified as a safety concern. The recommended dose of ceftobiprole is 500 mg administered in 250 mL saline (or other specified diluent) as a 2 h IV infusion every 8 h. It is recommended to the Delegate the PI should mention the size of this fluid load as it may have consequences for patients with heart failure and other conditions. The fluid load may also affect the important identified risk of hyponatraemia.

Recommendation 2: The safe and effective use of antibacterial agents depended on local conditions and testing for microbial susceptibility. It is recommended to the Delegate that the proposed indications should also include a statement such as, 'consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents', or words to that effect.

Recommendation 3: The 2007 European Medicines Agency (EMA) assessment of ceftobiprole medocaril stated that adverse effects in nonclinical studies due to impurities could not be completely excluded. The sponsor should provide an update on what risk minimisation activities have been employed to address this.

Recommendation 4: Ceftobiprole has not undergone clinical trial specifically for multi-drug resistant pneumonia, which will likely be a key use of the medicine. Routine pharmacovigilance activities should monitor this use.

Recommendation 5: The PASS study and the term 'immunocompromised patients' (as used in the important missing information entry in the safety summary), should include patients who had received lung transplants or patients with cystic fibrosis.

Suggested wording for conditions of registration***RMP***

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- Implement EU-RMP version 4.0 dated 21 July 2015 (data lock point 31 March 2015) with Australian Specific Annex version 2.0 dated 21 August 2015 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Zevtera is a sterile lyophilised powder for infusion and it containing ceftobiprole medocaril in a sodium citrate buffer system. The finished dosage form contains 666.6 mg of ceftobiprole medocaril sodium, 26.3 mg of citric acid monohydrate and approximately 10 mg sodium hydroxide (for pH adjustment) as a lyophilised powder in a 20 mL Type I glass vial with a fluoropolymer-coated bromobutyl stopper.

The drug substance is a pro-drug for the cephalosporin beta-lactam antibiotic ceftobiprole and the proposed product contains the equivalent of 500 mg of the active metabolite. The strength of the proposed product was initially expressed on the labels and elsewhere with respect to the quantity of the active antibiotic metabolite ceftobiprole (500 mg). This was not considered appropriate nor consistent with TGA practice and the company has now submitted labelling with respect to the prodrug (ie ceftobiprole medocaril sodium 667mg).

The product must be reconstituted and then further diluted prior to infusion. Is intended to be reconstituted with 10 mL water for injections or 5% dextrose to form a concentrate solution, which must be further diluted into an infusion bag or bottle containing 250 mL of 0.9% sodium chloride, 5% dextrose, or lactated Ringer's solutions for injection, before intravenous infusion over 2 h.

The recommended dose of Zevtera is 500 mg ceftobiprole (as 667mg ceftobiprole medocaril sodium) administered as a 2 h IV infusion every 8 h (2000 mg of ceftobiprole medocaril sodium per day).

All issues raised during the initial evaluation of this application have been satisfactorily resolved, apart from a minor revision to the PI.

From the quality and biopharmaceutic aspects, there is no objection to the registration of Zevtera (ceftobiprole medocaril sodium) 667mg powder for injection.

Nonclinical

Janssen-Cilag Pty Ltd had previously applied to register ceftobiprole medocaril sodium for the treatment of cSSTI. That application was withdrawn in Australia, although the submitted nonclinical data were evaluated. The assessment and summary sections of this report are based on both the previously evaluated data and the new nonclinical studies submitted with this application.

The newly submitted studies addressed the deficiencies in the previous submission. The major adverse findings from previously submitted studies were renal toxicity and convulsions. A new study showed that multiple hydrolytic enzymes, as well as non-enzymatic hydrolysis, contribute to the conversion of ceftobiprole medocaril to the active compound, ceftobiprole. Hence, pro-drug conversion is unlikely to be significantly affected by drug-drug interactions or by genetic polymorphisms that inactivate individual hydrolytic enzymes. Previously studies suggested that ceftobiprole medocaril is not extensively metabolised and is predominantly excreted in urine as the parental compound. Renal excretion of ceftobiprole is apparently not mediated by an active transport process in rats. New studies confirmed that exposure to the major plasma metabolite is minor in both rats and dogs. New studies also demonstrated that ceftobiprole is neither an inhibitor nor inducer of major human CYP activities. Previous results showed that ceftobiprole is neither a substrate nor inhibitor of most drug transporters tested, although it is a modest inhibitor of the hepatocyte uptake transporters OATP1B1 and OATP1B3. Overall, it appears unlikely that there would be significant pharmacokinetic interaction between ceftobiprole and co-administered drugs.

Previously evaluated repeat-dose toxicity studies showed that the major target organ for ceftobiprole medocaril in rats and marmosets, but not dogs, was kidney. Renal toxicity was associated with precipitation of drug-like material in the distal tubules. Convulsions occurred in some rats and marmosets exposed to high test article concentrations. In some cases, the convulsions may have been associated with impaired renal function. Histaminergic reactions were noted in dogs. Test article-related mortalities in rats and marmosets were associated with renal toxicity and with vascular reactions at the infusion site.

Previous studies suggested that ceftobiprole medocaril could show mutagenicity /clastogenicity under in vitro but not in vivo conditions. New studies support the conclusion that ceftobiprole medocaril, produced using the sponsor's current synthesis process, lacks mutagenic activity in the presence or absence of metabolic activation. No carcinogenicity studies were performed. This is considered acceptable given the relatively short treatment duration (maximum of 14 days) and the drug's limited/lack of activity in genotoxicity assays. Previously analysed reproductive toxicity data for rats and Cynomolgus monkeys suggested that ceftobiprole is neither a teratogen nor inducer of fetal/maternal toxicity.

Ceftobiprole medocaril drug product contains a large number of impurities. Although the sponsor has shown that current batches of ceftobiprole medocaril are not of genotoxic concern, many impurities have not been adequately qualified by repeat-dose toxicity studies and it is recommended that their levels be appropriately reduced or that toxicological studies that would allow qualification of higher impurity levels be performed. In their response, the sponsor has agreed to lower limits for two drug substance impurities and to a shorter shelf life (36 months reduced to 12 months) that allows lower limits for various degradants.

Overall, a number of minor deficiencies in the original submission have now been addressed. The basic conclusions from the previous assessment regarding (but not limited to) primary pharmacology, genotoxicity and reproductive toxicity remain unchanged. The lack of effects of ceftobiprole medocaril in tests for teratogenicity and fetal/maternal toxicity support its placement in Pregnancy Category B1. There are now no nonclinical objections to the registration.

Clinical

The submission contained the following clinical information:

- 21 clinical pharmacology studies (14 with PK data and 7 with PD (and PK/PD) data).

- 1 population PK analyses
- 2 Phase III pivotal efficacy/safety studies (Studies BAP248/307 and CAP-3001).
- 4 other efficacy/safety studies/reports including those conducted in cSSTI (these studies are not relevant to the requested indication in the current submission).

Pharmacokinetics (PK) and Pharmacodynamics (PD)

The submitted PK and PD studies is summarised in Tables 3 and 4 above. These studies showed that the systemic exposure of ceftobiprole is dose-proportional over a dose range of 125 to 1000 mg. Ceftobiprole exhibits linear and time-independent PK. Steady-state active substance concentrations are attained on the first day of dosing; no appreciable accumulation occurs with every 8 h dosing in subjects with normal renal function. Ceftobiprole's steady state volume of distribution (approximately 18 L) approximates the extra-cellular fluid volume and suggests intra-cellular penetration of ceftobiprole does not occur to an appreciable extent. The volume of distribution (V_{diss}) is dose and time independent.

Conversion from the pro-drug, to the active moiety ceftobiprole, occurs rapidly via non-specific plasma esterases. Ceftobiprole was primarily eliminated unchanged in urine. In Study 30982081-CSI-1004, approximately 83% of the dose was excreted as unchanged ceftobiprole in urine and approximately 5% of the dose was excreted in urine as the open ring metabolite. As ceftobiprole does not appear to undergo significant hepatic metabolism, no PK study in hepatic impairment was conducted. Ceftobiprole is excreted in urine by glomerular filtration and does not undergo renal tubular secretion. The terminal elimination half-life is about 3 h. The effects of renal impairment on the PK were investigated in a single-dose study (BAP00018). Systemic exposure was 1.3 times, 2.5 times and 3.3 times higher in subjects with mild, moderate and severe renal impairment, respectively, than in subjects with normal renal function. In subjects with renal impairment, systemic clearance correlated well with creatinine clearance (CrCl). As ceftobiprole is primarily eliminated by renal excretion, dosage adjustments in renal impaired patients were optimised by simulations and modelling, and evaluated in the Phase III programme. The table below shows the dose and dose interval adjustments evaluated.

Table 9: Ceftobiprole dose adjustments based on creatinine clearance

Renal function	CL _{CR} (mL/min) ^a	Recommended dose ^b
Normal	> 80	500 mg 3 times daily (q8h)
Mild	50 to 80	500 mg 3 times daily (q8h)
Moderate	30 to < 50	500 mg twice daily (q12h)
Severe	10 to < 30	250 mg twice daily (q12h)

^a The Cockcroft-Gault formula using actual body weight was the recommended method for estimating CL_{CR} in the ceftobiprole clinical studies.

^b All doses administered as a 2 hour i.v. infusion.

The 500 mg dose refers to the active metabolite (ceftobiprole) which is equivalent to 667 mg parent drug (ceftobiprole medocartil). In this document, the 500 mg ceftobiprole is used to represent the 667 mg ceftobiprole medocartil sodium.

Simulation and experience in end stage renal disease (ESRD) subjects suggested that a dose of 250 mg ceftobiprole (2 h infusion post-dialysis) every 24 h (q24h) is an appropriate regimen.

The influence of the age, gender, race and body weight of patients was explored in the population PK analysis. These factors were not identified as clinically relevant covariates.

It is not considered necessary to adjust the dose on the basis of age, gender, race, and body weight.

Clinical drug interaction studies have not been conducted as the overall likelihood of significant interactions is considered minimal based on its PK. Conversion from the prodrug to the active drug ceftobiprole is rapid and complete, and a literature review confirms that administration of concomitant medications is not known to reduce Type A esterase activity. Since protein binding of ceftobiprole is low (16%) and independent of concentration, displacement interactions are not anticipated. As ceftobiprole is not extensively metabolised, does not induce CYP450 isoenzymes and minimally inhibits CYP450 isoenzymes, drug-drug interactions are not anticipated. As ceftobiprole is neither a substrate nor inhibitor of p-glycoprotein, transport-related interactions are also not anticipated. Ceftobiprole is primarily excreted unchanged in urine by glomerular filtration; a fraction of the drug is reabsorbed; ceftobiprole does not undergo renal tubular secretion, as evidenced from an interaction study with probenecid in a rat model. Ceftobiprole should therefore not affect the tubular secretion of other agents. Exploratory population PK screening indicate concomitant administration of fentanyl, lidocaine, paracetamol, diclofenac, aspirin, heparin, diphenhydramine, propofol, hydromorphone hydrochloride, methadone, hydrocodone bitartrate, metamizole sodium, furosemide did not impact on the PK of ceftobiprole.

The submitted PD studies are summarised in Table 5 above. The primary PD effects in terms of established EUCAST MIC breakpoints are described in the table below.

Table 10: Clinical breakpoint by EUCAST

Pathogen	Minimum Inhibitory Concentrations (µg/mL)	
	≤ S	R >
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	2	2
<i>Streptococcus pneumoniae</i>	0.5	0.5
Enterobacteriaceae	0.25	0.25
<i>Pseudomonas aeruginosa</i>	I:E ^a	I:E ^a
Non-species specific breakpoint ^b	4	4

^aInsufficient evidence

^bBased on the PK/PD target for Gram-negative organisms

Evidence for ceftobiprole's antibacterial activity is based on approximately 120000 surveillance isolates relevant to bacterial pneumonia from North America, Latin America, EU, Asia-Pacific, China and tested for susceptibility. Collective surveillance data show ceftobiprole has low MIC₉₀ (minimum Inhibitory concentration required to inhibit the growth of 90% of organisms) values (≤ 4 µg/mL) for a wide variety of important gram positive and negative pathogens relevant to HAP and CAP, that is, *Staphylococci*, *S. pneumoniae*, and *H. influenzae*; MIC₅₀ values ≤ 4 µg/mL for *Enterobacteriaceae* and many surveillance *P. aeruginosa* isolates. Its spectrum of activity against gram negatives is similar to extended spectrum cephalosporins. In addition, ceftobiprole is active against MRSA and penicillin and ceftriaxone resistant pneumococci. The MIC₉₀ is ≤ 2 µg/mL across many studies and surveillance programs conducted in different regions of the world. Ceftobiprole is also active against surveillance isolates of MRSA with VISA (vancomycin-intermediate *Staph. aureus*) and linezolid-resistant phenotypes. Ceftobiprole has MIC values ≤ 4 µg/mL against penicillin and ceftriaxone resistant pneumococci, and vancomycin-resistant/ampicillin-susceptible *E. faecalis*.

Effect on the intestinal microflora is discussed in the CER (Attachment 2). The secondary impact on faecal flora and selection for organisms such as *C. difficile*, have been studied but only in the short term and faecal samples were not collected routinely in the pneumonia studies. The changes in aerobic intestinal microflora and anaerobic intestinal microflora were within normal variation. No new colonising aerobic and anaerobic bacteria resistant to ceftobiprole (MIC > 4 µg/mL) found.

Effect on ECG is discussed in the CER (Attachment 2). The QT/QTc prolongation³⁹ effect of single IV ceftobiprole at therapeutic and supra-therapeutic doses was no worse than that of placebo. No AEs reported suggestive of pro-arrhythmic potential.

Clinical efficacy

No dose-finding studies were conducted and the dosing selection was based on animal models. Animal models demonstrate T>MIC is the PK/PD driver for ceftobiprole efficacy. For coverage including gram-negative pathogens the magnitude of %fT >MIC should be ≥50%. Using population PK approaches, projected and estimated probability of target attainment (PTA) demonstrate the adequacy of the 2 h infusion of 500 mg tds dosing for broad spectrum coverage in HAP. The retrospective analysis showed that the observed PK/PD targets and parameters from these models were predictive of microbiological and clinical response in Study BAP248/307.

Study BAP248/307 Hospital-acquired pneumonia (HAP)

This is a randomised, double-blind, multicentre, non-inferiority study, and the primary objective was to demonstrate non-inferiority of ceftobiprole versus linezolid+ceftazidime with respect to the clinical cure rate at the Test of Cure (TOC) visit in subjects with Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Study population were adults hospitalised with HAP (including VAP). The inclusion criteria are detailed in the CER (Attachment 2). The planned numbers of subjects were 770. Study treatments were ceftobiprole medocaril (500 mg tds as a 2 h IV infusion), or linezolid (600 mg twice a day (bd) as a 1 h IV infusion) + ceftazidime (2 g tds as a 2 h IV infusion) for 7 to 14 days. Subjects were randomly assigned in a 1:1 ratio to either group. Combination therapy with protocol defined agents (levofloxacin, amikacin, or gentamicin) is permitted if there is a risk of pseudomonal infection.

The primary efficacy outcome was clinical cure rate at the TOC visit, defined as the ratio of the numbers of subjects with clinical outcome of 'Cure' to the total numbers of subjects in the analysis set under consideration. The primary efficacy analysis (non-inferiority of ceftobiprole versus linezolid+ceftazidime) was performed on the co-primary Clinically Evaluable and Intent-to-Treat (ITT) analysis sets.

Secondary efficacy analyses (non-inferiority of ceftobiprole versus linezolid+ceftazidime) with respect to the following outcomes were performed using a step-down procedure in the following order:

1. Microbiological eradication rate at the TOC visit,
2. Clinical cure rate at TOC in subjects with HAP caused by *S. aureus* (including MRSA),
3. Clinical cure rate at the TOC visit in subjects with VAP,
4. Clinical relapse rate at the LFU visit in subjects with HAP,
5. 30 day pneumonia-specific mortality rates in subjects with HAP.

Analysis populations include ITT, microbiological Intent-to-Treat (mITT), Clinically Evaluable (CE) and Microbiologically Evaluable (ME) population. A 15% non-inferiority

³⁹ In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical [depolarization and repolarization of the ventricles](#). A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted (QTc) to improve the detection of patients at increased risk of ventricular arrhythmia.

margin was prospectively defined, in accordance with the CHMP Guideline.⁴⁰ The justification for the 15% non-inferiority margin was discussed in the CER (Attachment 2).

A total of 781 subjects were randomised. 251 (64%) in the ceftobiprole group and 244 (63%) in the linezolid/ceftazidime group were considered clinically evaluable for efficacy. A total of 571 subjects were enrolled with HAP (excluding VAP) with 287 in the ceftobiprole group and 284 in the comparator group. Some 210 subjects (27%) were enrolled with VAP; majority of subjects with VAP (77%) were mechanically ventilated for ≥ 5 days. Some 67% of all subjects were male; mean age 60.6 years. Some 69% had valid baseline pathogens, of these, 36% were gram-positive, 48% gram-negative, 24% with polymicrobial infection. There was a baseline imbalance with respect to gender between the 2 arms (the % of males in the ceftobiprole and linezolid/ceftazidime group were 71% versus 62%). All other demographic and baseline characteristics were similar for subjects in the ITT set.

As expected, patient characteristics were different between VAP subjects and HAP (excluding VAP) subjects. Subjects in the VAP group were about 10 years younger, and with a higher proportion of males, subjects with thoracic trauma, APACHE II scores ≥ 15 , CRP levels >100 mg/L, albumin levels ≤ 25 g/L and supra-normal creatinine-clearance (≥ 150 mL/min). More VAP subjects had gram-negative or polymicrobial infections, infections with *MSSA*, *P. aeruginosa* or *Acinetobacter species* and more VAP subjects received antipseudomonal treatment. Compared to VAP subjects, HAP (excluding VAP) subjects had a higher baseline prevalence of systemic inflammatory response syndrome (SIRS) and of medical co-morbidities and renal impairment (CrCl <50 mL/min) and more frequent chronic care utilisation.

Within the VAP subgroup, mean age was lower in the ceftobiprole group (51.7 years versus 55.3 years), and the proportion of younger VAP subjects (aged <45 years) was 38% in the ceftobiprole arm and 29% in the comparator arm. Further differences ($>5\%$) were apparent in the VAP subgroup; baseline prevalence of SIRS, CRP >100 mg/L, albumin ≤ 25 g/L, APACHE II score ≥ 15 , use of anti-pseudomonal antibiotics, valid gram negative pathogens and polymicrobial infections were all more frequent in the ceftobiprole group. Emphysema, use of antibiotics within 24 h prior to baseline and long-term ventilation were more frequent in the linezolid/ceftazidime group. Additional medical review of patient profiles showed notable imbalances in the VAP subgroup related to head trauma and polytrauma. A similar % of subjects did not complete the study in each treatment group. The distribution of subjects by reasons for discontinuation was similar between the treatment groups, with the most common reason being death.

Results for the primary efficacy outcome

The clinical cure rate at the TOC visit in the Clinically Evaluable and ITT analysis sets was similar between the 2 groups. Clinical cure rates were 69.3% versus 71.3% (Clinically Evaluable Set) and 49.9% versus 52.8% (ITT set) in the ceftobiprole and comparator groups respectively. The lower limit of the 2-sided 95% confidence interval (CI) for the difference was -10% (within -15%). Non-inferiority of ceftobiprole versus linezolid/ceftazidime was also demonstrated in the pre-specified subgroup of subjects with HAP (excluding VAP). The reasons for failure were similar between the 2 groups in clinically evaluable set (subjects may have had ≥ 1 reason), that is, use of non-study systemic antibiotics for pneumonia (21.5% in ceftobiprole-group and 18.9% in the comparator group); deemed clinical failures at TOC visit by investigators (16.7% in ceftobiprole group and 16.8% in comparator group); TOC visit assessment was missing and final assessment before TOC was 'worsened'/'unchanged' from baseline (9.6% of in the ceftobiprole group and 6.1% in the comparator's group). In addition, during the course of the study, 7 sites were identified as being at risk for having made errors in study

⁴⁰ EMEA/ CPMP/EWP/2158/99. Guideline on the choice of the non-inferiority margin.

conduct. A sensitivity analysis excluding all subjects from these sites confirmed the findings of the primary analysis.

Table 11: Clinical cure rate at TOC (primary endpoint) in Study BAP248/307

<u>Analysis set</u> <u>Group</u>	Ceftobiprole		Linezolid/ceftazidime		Diff. (%)^a	95% CI[#]
	N	n (%)	N	n (%)		
<u>Intent-to-Treat</u>						
All subjects	391	195 (49.9)	390	206 (52.8)	(-2.9)	(-10.0; 4.1)
NP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	(0.8)	(-7.3; 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	(-13.7)	(-26.0; -1.5)
<u>Clinically Evaluable</u>						
All subjects	251	174 (69.3)	244	174 (71.3)	(-2.0)	(-10.0; 6.1)
NP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	(1.6)	(-6.9; 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	(-18.2)	(-36.4; -0.0)

However, non-inferiority of ceftobiprole was not demonstrated in the subset of VAP subjects. In VAP subjects, clinical cure rates in the clinically evaluable analysis set were 37.7% (20/53) in the ceftobiprole group and 55.9% (33/59) in the comparator group. Similar to the results for all subjects, for both non-VAP and VAP subjects the primary reason for failure was the use of non-study systemic antibiotics for pneumonia and the second most common reason was that subjects were deemed clinical failures at the TOC visit. Similar to the results in the clinically evaluable set, there was a significant difference in the ITT set in the clinical cure rates between the 2 groups with respect to the ventilation status for the non-VAP and VAP subject stratum. The trend toward lower cure rates in the ceftobiprole group versus comparator group that was observed in VAP subjects was not observed in non-VAP subjects, regardless of whether they were never ventilated or were ventilated < 48 h prior to the onset of pneumonia. Based on the different outcomes, and the fact that VAP represents a different disease entity (different patient characteristics with regard to co-morbidities and clinical prognosis), the majority of efficacy analyses that were planned to be performed on all subjects were also performed separately on HAP (excluding VAP) subjects and VAP subjects.

Results for other efficacy outcomes

1. Microbiological eradication rates (MER) at the TOC visit

In the Microbiologically Evaluable set, MER at the TOC visit were lower (53.7% versus 62.4%) in the ceftobiprole group. The 95% CI for the difference was -19.2% to 1.9%, non-inferiority was not demonstrated. This result was primarily driven by lower MER in the VAP subgroup* (see below). The lower limit of the 95% CI for the difference in MER in the HAP subjects (excluding VAP) was close to the 15% margin (that is, -15.3% in the MITT set and -16.7% in Microbiologically Evaluable set).

Table 12: Microbiological eradication rate at TOC visit

<u>Analysis set</u> <u>Group</u>	Ceftobiprole		Linezolid/ceftazidime		Diff (%)^a	95% CI[#]
	N	n (%)	N	n (%)		
<u>Microbiological Intent-to-Treat</u>						
All subjects	269	105 (39.0)	267	127 (47.6)	(-8.5)	(-16.9; -0.2)
NP (excluding VAP)	179	87 (48.6)	181	97 (53.6)	(-5.0)	(-15.3; 5.3)
VAP	90	18 (20.0)	86	30 (34.9)	(-14.9)	(-27.9; -1.9)
<u>Microbiological Evaluable</u>						
All subjects	162	87 (53.7)	170	106 (62.4)	(-8.6)	(-19.2; 1.9)
NP (excluding VAP)	116	73 (62.9)	120	81 (67.5)	(-4.6)	(-16.7; 7.6)
VAP	46	14 (30.4)	50	25 (50.0)	(-19.6)	(-38.8; -0.4)

n = number of subjects with microbiological eradication at the TOC visit.

^a Difference ceftobiprole minus linezolid/ceftazidime.

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

*Among VAP subjects who were microbiologically evaluable, MER at the TOC visit were 30.4% (14/46) for the ceftobiprole group and 50.0% (25/50) for the comparator group. The 95% CI for the difference in microbiologically evaluable VAP subjects was -38.8% to -0.4%. Of the 46 VAP subjects in the ceftobiprole group who were microbiologically evaluable at the TOC visit, only 13 (28.3%) subjects had documented cultures at the TOC visit. The microbiological outcome of the remaining 33 subjects was derived from the clinical outcome. In contrast, 23 of 50 (46.0%) subjects had a documented culture at the TOC visit in the comparator group.

Per-pathogen clinical cure rates for HAP subjects (excluding VAP) in the Microbiologically Evaluable Set were similar between the 2 groups for pathogens isolated from 10 or more subjects.

2. 30 day pneumonia-specific mortality rate

Pneumonia-specific mortality at 30 days was a pre-specified secondary endpoint. In addition, 30-day all-cause mortality was also analysed. All-cause mortality rates and pneumonia-specific mortality rates were similar between the groups in ITT analysis set. Pneumonia-specific mortality was similar between the groups in HAP (excluding VAP) subjects and VAP subjects. However, there was a trend towards a lower all-cause mortality rate with the comparator in the VAP subgroup, while all-cause mortality was numerically higher with the comparator in HAP (excluding VAP) subjects.

3. Clinical relapse at the late follow-up visit

This occurred in 4.6% of the ceftobiprole group and 4.5% of the comparator group. Microbiological relapse at the late follow-up visit occurred in 3.8% of the ceftobiprole group and 3.1% of the comparator group.

Study 30982081-CAP-300.1 Community-acquired pneumonia (HAP)

This is a randomised, double-blind, multicentre study. The primary objective was to demonstrate non-inferiority of ceftobiprole versus ceftriaxone ± linezolid with respect to clinical cure rates at the TOC visit in subjects hospitalised with CAP. Study population were adults hospitalised with CAP and requiring IV antibiotics for ≥ 72 h. The study treatment were ceftobiprole medocaril (500 mg ceftobiprole tds as a 2 h IV infusion), or ceftriaxone (2g QD as a 0.5 h IV infusion) ± 600 mg linezolid every 12 h as a 1 h IV infusion, for 5 to 14 days. Subjects were randomly assigned in a 1:1 ratio. A switch from IV to oral cefuroxime axetil (500 mg bd) was allowed after a minimum of 3 days of IV therapy for subjects who met all protocol-specified criteria for improvement and were candidates for discharge. The total treatment duration was a minimum of 5 days and a target of 7 days. If a subject required additional days of therapy, the duration could have been extended up to 10 days. Therapy could have been further extended to 14 days for subjects with a history of persistent bacteraemia or necrotizing pneumonia. Linezolid was to be added to ceftriaxone for subjects with confirmed ceftriaxone-resistant *S.pneumoniae* provided the susceptibility of the isolate to linezolid had been confirmed. Linezolid was added to ceftriaxone when the incidence of MRSA in CAP isolates was prevalent (>15%), or when the subject's initial signs and symptoms were suggestive of *S. aureus* infection.

The primary efficacy endpoint was the clinical cure rate at the TOC visit, defined as the ratio of the number of subjects who had a derived clinical outcome of Cure at the TOC visit to the total number of the subjects in the analysis set under consideration. The submitted justification regarding the 10% non-inferiority margin is considered acceptable.

A total of 666 subjects were randomised and 638 were analysed. The ITT analysis set comprised 314 subjects randomised to ceftobiprole and 324 to ceftriaxone ± linezolid. Of the 638 subjects, 231 (74%) in the ceftobiprole group, and 238 (73%) in the combination group were considered clinically evaluable. In the ITT analysis set, there were no significant between group differences with respect to demographic and baseline

characteristics. Demographic and baseline characteristics for subjects in the Clinically Evaluable analysis set were consistent with those of the ITT set. A valid baseline pathogen was isolated from 184 (29%) of 638 subjects in the ITT set: 101 subjects (16%) had ≥ 1 gram positive pathogen, and 100 subjects (16%) had ≥ 1 gram negative pathogen. Sixteen patients in ceftobiprole group and 8 in the combination group had polymicrobial infection. Some 11% of subjects received concomitant linezolid treatment, 48% of subjects (307/638) were in PORT Risk Classes III–V (PSI score ≥ 71) and 22% of subjects (141/638) were in PORT Risk Classes IV–V (PSI score ≥ 91). A similar % of subjects did not complete the study in each group: 18% in the ceftobiprole group and 15% in the ceftriaxone with or without linezolid group.

Results for the primary efficacy outcome

Non-inferiority of ceftobiprole compared with ceftriaxone \pm linezolid was demonstrated within the 10% non-inferiority margin for the clinical cure rate at the TOC visit for both the clinically evaluable and ITT co-primary analysis sets. Clinical cure rates at the TOC visit were 86.6% and 87.4% in the ceftobiprole and ceftriaxone \pm linezolid groups, respectively, in the Clinically Evaluable analysis set and 76.4% and 79.3%, respectively, in the ITT analysis set. Non-inferiority was also shown for the subgroup of subjects in PORT Risk Classes \geq III (PSI score ≥ 71) and PORT Risk Classes \geq IV (PSI score ≥ 91).

Table 13: Clinical cure at TOC (primary endpoint) in CAP-3001

Analysis set Group	Ceftobiprole		Ceftriaxone \pm linezolid		Diff. (%) ^b	95% CI [#]
	N	n (%)	N	n (%)		
Intent-to-Treat						
All subjects	314	240 (76.4)	324	257 (79.3)	(-2.9)	(-9.3; 3.6)
PORT Risk Classes \geq III	158	125 (79.1)	149	117 (78.5)	(0.6)	(-8.6; 9.7)
PORT Risk Classes \geq IV	69	56 (81.2)	72	56 (77.8)	(3.4)	(-9.9; 16.7)
Clinically Evaluable						
All subjects	231	200 (86.6)	238	208 (87.4)	(-0.8)	(-6.9; 5.3)
PORT Risk Classes \geq III	126	109 (86.5)	117	101 (86.3)	(0.2)	(-8.4; 8.8)
PORT Risk Classes \geq IV	51	46 (90.2)	58	49 (84.5)	(5.7)	(-6.7; 18.1)

n is the number of subjects with clinical cure at the TOC visit.

^a Difference ceftobiprole minus linezolid/cefazidime.

^b Difference ceftobiprole minus ceftriaxone with or without linezolid.

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

Results for other efficacy outcomes

The secondary endpoints were evaluated using a step-down hierarchical procedure in the following order:

1. Microbiological eradication rate at TOC visit
2. Clinical cure rate at TOC visit for those with PSI score ≥ 91 ;
3. The 30 day pneumonia-specific mortality rates

A 15% non-inferiority margin was used to test all secondary hypotheses. Non-inferiority of ceftobiprole versus ceftriaxone \pm linezolid was demonstrated for all three pre-specified secondary efficacy endpoints.

1. Microbiological eradication rates

Some 88.2% (60/68 subjects) in the ceftobiprole group and 90.8% (69/76) in the ceftriaxone \pm linezolid group in the Microbiologically Evaluable analysis set (2-sided 95% CI for the difference of ceftobiprole minus ceftriaxone \pm linezolid: -12.6% to 7.5%).

2. 30 day all-cause mortality (ITT)

Some 1.6% in the ceftobiprole group and 2.5% in comparator arm. 30 day pneumonia-specific mortality was 0.3% in ceftobiprole group and 0.9% in the ceftriaxone \pm linezolid group.

3. Clinical cures

Clinical cures was observed for 26 (93%) of 28 subjects with *S. pneumoniae* in the ceftobiprole group, including cures for both subjects with MDR (multi-drug resistance) *S. pneumoniae*. Clinical cures observed for all 7 subjects in the ceftobiprole group with *S. aureus* at baseline, including 1 MRSA. Clinical cures observed for all subjects who had *H. influenzae*, *E. coli*, *M. catarrhalis*, *K. oxytoca*, or *Acinetobacter* species isolated at baseline. Clinical cures observed for 6 (67%) of 9 subjects with *H. parainfluenzae* and 4 (80%) of 5 subjects with *K. pneumoniae*. The microbiological eradication rates for the pathogens listed above were similar to the clinical cure rates for subjects with those pathogens.

Clinical safety

There are 25 completed clinical studies, with 539 subjects in 20 Phase I studies, 40 cSSTI subjects in the Phase II study BAP00034, 632 CAP subjects in CAP-3001, 772 subjects with HAP in BAP248/307 and 1,593 cSSTI subjects in 2 Phase III studies BAP00154 and BAP00414. Safety data from CAP-3001 and BAP248/307 were analysed both by study and in an integrated overall safety analysis. Safety data from the 2 cSSTI Phase III and single cSSTI Phase II studies were integrated for analysis and compared with the pooled analysis of safety data from the 2 Phase III pneumonia studies. See Tables 5 and 6 above for details.

In Study BAP248/307, the overall incidences of AEs, SAEs, AEs that led to discontinuation, TRAEs were comparable between the two treatment groups. The percentage of subjects in each treatment group who reported ≥ 1 TEAE was similar (77% of ceftobiprole treated and 78% of linezolid/ceftazidime-treated subjects). Some 25% of subjects in both treatment groups had ≥ 1 AE considered to be treatment-related and 23% in the ceftobiprole group and 22% in the linezolid/ceftazidime group died during the course of the study.

In Study CAP-3001, there were no significant differences observed between the treatment groups in the overall incidence of AEs, deaths, SAEs or discontinuations due to AEs. TRAEs were more in the ceftobiprole group largely due to higher rates of treatment-related nausea (7% versus 2%, respectively) and vomiting (5% versus 2%). TRAEs considered serious or leading to treatment discontinuation were not significantly different between groups.

In the pooled Phase III pneumonia studies, 74.1% of all ceftobiprole-treated subjects and 71.8% of all comparator-treated subjects experienced at least 1 AE. A total of 29.7% of all ceftobiprole treated subjects and 25.6% of all comparator treated subjects experienced ≥ 1 drug-related AE. Most commonly (in $\geq 1\%$ of those treated with ceftobiprole): nausea (4.3% of subjects), diarrhoea (4.2%), vomiting (3.3%), hyponatraemia (2.7%), phlebitis (2.3%), dysgeusia (1.6%), headache (1.4%), rash (1.1%), ALT increased (1.1%) and AST increased (1.0%).

Identified risks for ceftobiprole include the followings

- hypersensitivity reactions
- anaphylactic reactions
- hepatic enzyme elevations
- hyponatraemia
- pseudomembranous colitis/ *C. difficile* colitis
- injection/infusion-site reactions
- localised fungal infections.

The safety of ceftobiprole was also evaluated in special populations by age, gender, race, renal impairment and hepatic impairment. Analysis of these special populations revealed

no particular safety signal of concern especially in the HAP study, where patients were generally much sicker. The dose of ceftobiprole should be adjusted, as recommended, for patients with moderate to severe renal impairment. The safety and efficacy of ceftobiprole in children aged birth to <18 years have not yet been established. There is an ongoing Paediatric investigation programme.

There have been a total of 199 deaths in the ceftobiprole development program (Table 14).

Table 14: Number of deaths in the ceftobiprole development program

	Ceftobiprole	Comparator
Study BAP248/307	88/386 (22.8%)	84/386 (21.8%)
Study CAP-3001	9/310 (2.9%)	9/322 (2.8%)
Phase 3 cSSTI studies	3/972 (0.3%)	4/661 (0.6%)
Phase 1 (ICU study)	2	0

Post marketing experience

Based on the 14,380 vials (500 mg) of ceftobiprole distributed worldwide since launch, estimated exposure is 5,036 person-days. Assuming average treatment duration was 7 days, <1,000 subjects receiving ceftobiprole during the marketing period. During the period of ceftobiprole licensed use in cSSTIs, <1,000 subjects were exposed to ceftobiprole. There were 6 spontaneous cases reports from this period: 3 cases from Health Canada Pharmacovigilance of fits; 1 case of acute tubular necrosis; 1 case of pancytopenia and diffuse maculopapular rash; 1 case of agranulocytosis recognised after 18 days therapy and resolving after ceftobiprole discontinuation.

Risk of the emergence of resistance

The clinical program did not reveal any worrisome signal in regards to the selection of resistance but relatively few patients have been exposed over only a short period of time. Broad spectrum cephalosporins are recognised to increase the risk of *C. difficile* colonisation and colitis; it would be expected that Zevetra would be no different in this regard.

The sponsor has provided the mandated Risk Assessment of Microbial Resistance. The comments from the clinical evaluator are detailed in CER (Attachment 2). Overall, the clinical evaluator is of the view that the real risk of developing resistance to cephalosporins is low and the reason is as follows:

1. It is difficult for *Staphylococcal* and *Streptococcal* species to develop resistance and even very resistant species remain susceptible to the drug;
2. Mechanisms of resistance to various gram negatives have been defined; some of these highly resistant strains are already resistant to the drug so ceftobiprole is unlikely to make the situation worse;
3. The sponsor has projected the expected use of ceftobiprole in Australia. Use in 2016 is expected to be in 50 patients rising to 2650 in 2020, average number of days of dosing will be 8. There will be very restricted use of the drug (small numbers and short exposure), and this means the risk of dissemination of ceftobiprole resistant strains is low;
4. The clinical development program confirms that using the recommended dose of 500 mg tds as a 2 h IV infusion has high coverage of the target pathogens isolated during the 2008 surveillance study.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of the drug for nosocomial (hospital-acquired) bacterial pneumonia (excluding ventilator-associated pneumonia) and community acquired bacterial pneumonia requiring hospitalisation.

RMP evaluation and the ACSOM recommendations

In the first round evaluation, the RMP evaluator has requested that the sponsor should include at least 6 Australian sites in the monitoring system to ensure the surveillance studies of clinical isolates adequately reflect the local situation. Representation should include isolates from different Australian institutions rather than many isolates from few sites. In their response, the sponsor states that they intend to set up annual surveillance programmes on *S. aureus* and *Enterobacteriaceae* for ceftobiprole in collaboration with the Australian Group on Antimicrobial Resistance, once the commercial sponsor for Zevtera in Australia has been defined and local pharmacovigilance activities have been established. The surveillance program will include at least six Australian sites in the monitoring system and will include isolates from different Australian institutions.

This submission was discussed at the ACSOM meeting. Of note, the ACSOM considers that potential fluid overload is a safety concern and recommends that the PI should mention the size of this fluid load as it may have consequences for patients with heart failure and other conditions and the fluid load may also affect the important identified risk of hyponatraemia. The ACSOM considers that the safe and effective use of antibacterial agents depended on local conditions and testing for microbial susceptibility and recommends that the indications should include a statement such as, '*consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents*'. These recommendations have been accepted by the sponsor and the PI has been revised.

The RMP evaluator suggested that any changes to the RMP which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. The following wording has been suggested as conditions of registration:

- Implement EU-RMP version 4.0 dated 21 July 2015 (data lock point 31 March 2015) with Australian Specific Annex version 2.0 dated 21 August 2015 and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

PK and PD

Ceftobiprole has potent activity in nonclinical models against the most common pathogens causing CAP and many of those causing HAP. Ceftobiprole appears to be bactericidal and with high penetration into tissues of relevance, that is the lung. Ceftobiprole has a straightforward PK profile and aside from reduced dosing in renal impairment, there is low risk of drug-drug interactions.

Treatment of HAP

For the treatment of HAP, Study BAP248/307 met the primary objective of demonstrating the non-inferiority of ceftobiprole to a 'standard-of-care' active comparator. However, the clinical evaluator pointed out that the choice of comparator in this study is probably still not standard-of-care in most centres. Assumptions had to be made about the expected clinical cure rates of the comparator arm, as ceftazidime and linezolid had never been

partnered together (at least not then) in a clinical trial. While there is robust evidence that ceftobiprole is as efficacious as ceftazidime+linezolid as measured by clinical cure rates, pneumonia-specific mortality and all-cause mortality in HAP, this is only true if the VAP subjects are excluded. While BAP248/307 only enrolled a relatively small subset of VAP subjects, clinical cure and microbiological eradication rates in VAP subjects at the TOC visit were lower and all-cause mortality numerically higher, in the ceftobiprole group than in the linezolid/ceftazidime group, although none of these differences were statistically significant. The reasons that the VAP subjects in the comparator group performed better than the VAP subjects in the ceftobiprole group are yet to be determined. The US FDA has recently amended its regulatory guidelines for hospital-acquired pneumonia and VAP such that separate studies are required for VAP subjects. This amendment recognises the heterogeneity within the study population and the ways to try and overcome these through stratification by APACHE II score and time of onset of VAP after onset of mechanical ventilation.

There is a numerical imbalance in microbiological eradication rates (MER) in this study, with a lower percentage of subjects in the ceftobiprole group achieving eradication. It is noted that a limited number of microbiological samples were available at TOC visit; therefore microbiological outcome was presumed based on clinical outcome in most cases. When VAP is excluded, microbiological eradication rates were similar in the two treatment groups for gram positive bacteria and most of the gram negative pathogens. For the relatively small sample of *Haemophilus* and *Acinetobacter* species at baseline, numerically lower clinical cure and microbiological eradication rates were observed, in both the VAP and HAP (excluding VAP) subgroups.

Treatment of CAP

For the treatment of subjects hospitalised with CAP, Study CAP-3001 demonstrate that ceftobiprole is as effective as a high dose of 2 g ceftriaxone once a day ± linezolid. In patients with CAP, ceftobiprole medocaril was effective in those at risk for poor outcomes (pneumonia severity index ≥ 91, Pneumonia Patient Outcomes Research Team score IV-V or bacteraemic pneumonia). The most prevalent pathogen identified was *S. pneumoniae* but importantly it was only found in 28 subjects, that is, a very small number overall. While cure rates were very high, the issue is that culture positive bacterial pneumonia occurs in the minority using traditional techniques, sequencing in blood may overcome some of these issues in future trials if such results can be provided real-time. Clinical cures for other important CAP pathogens in the ceftobiprole group included 7 (100%) *Staph.aureus*; 6 (100%) with *E. coli*, 4 (80%) with *K. pneumoniae*, 1 (100%) with *K. oxytoca*, 4 (100%) with *M. catarrhalis*.

Benefits risks balance

Ceftobiprole medocaril can be given as monotherapy which avoids the use of two or more antibiotics. Ceftobiprole monotherapy offers a simplified option for the initial empirical treatment of patients with HAP (excluding VAP) and in those with CAP requiring hospitalisation. Ceftobiprole has a favourable PK profile with rapid mode of action, linear PK and no accumulation seen; there is little potential for drug-drug interactions. Ceftobiprole is a broad-spectrum antibiotic with potent gram positive (including for MRSA) and gram negative activity against the common pneumonia-causing bacteria. Alternative agents such as linezolid, while an excellent gram positive antibiotic, have idiosyncratic haematological and neurological AEs. To date no such idiosyncratic reactions have been seen with ceftobiprole, but patient exposure is limited. Other broad-spectrum penicillins (such as Timentin®) are well tolerated but do not have MRSA activity in which case they are often combined with glycopeptides or linezolid if MRSA is suspected.

Ceftobiprole is associated with a number of GI toxicities especially nausea and altered taste. Ceftobiprole has to be given IV as a 2 h infusion 3 times per day, this is a major

disadvantage. The potential for the drug to interfere with some forms of testing for creatinine may be an issue, especially in those with renal impairment for whom dose adjustment is required; in addition, there is no equivalent drug for oral administration as a step-down option. The step-down option in the CAP study was a first generation cephalosporin.

Ceftobiprole resistance may occur for reasons not directly related to the use of the drug in Australia, for example global movement of very resistant pathogens as people travel. In Australia, the incidence of resistance in CAP organisms is growing but it still remains relatively low. The concern is that when ceftobiprole is approved for use in CAP, the drug will be used empirically and not stopped even when the organism is revealed to be sensitive to narrower spectrum agents. If the drug is misused on a global scale, then there is a risk of the selection of increasingly resistant organisms.

The Delegate considers the overall risk benefit balance is positive for the proposed use.

Summary of issues

Study BAP248/307 is the single pivotal study that assessed the efficacy and safety of Zevtera for the treatment of hospital-acquired pneumonia (HAP). In the subset of subjects with ventilator-associated pneumonia (VAP), the clinical cure and microbiological eradication rates were lower and all-cause mortality numerically higher in the Zevtera group than in the comparator (linezolid/ceftazidime) group.

Study CAP-3001 is the single pivotal study that assessed the efficacy and safety of Zevtera for the treatment of community-acquired pneumonia (CAP). Non-inferiority of Zevtera compared with ceftriaxone ± linezolid was demonstrated for the clinical cure rate, for both the clinically evaluable and ITT co-primary analysis sets.

Preliminary action proposed by the Delegate

The Delegate had no reason to say, at this time, that the application for Zevtera should not be approved for the revised indications.

Any changes to the RMP which the sponsor agreed will become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The conditions of registration are as follows:

- Implement EU-RMP version 4.0 dated 21 July 2015 (data lock point 31 March 2015) with Australian Specific Annex version 2.0 dated 21 August 2015 and any future updates as a condition of registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACPM consider that the data from Study BAP248/307 is sufficient to support the use of Zevtera for the treatment of HAP, excluding VAP (ventilator-associated pneumonia)? Does ACPM consider that the comparator (ceftazidime+linezolid) used in this study is an appropriate comparator?
2. Does ACPM have concerns about the numerical imbalance in microbiological eradication rates (MER) with a lower percentage of subjects in the Zevtera group achieving microbiological eradication (Study BAP248/307)?

3. What is the view of the ACPM with regards to the potential risk of developing antibiotics resistance to Zevtera? Does ACPM have any specific recommendation with regards to the antimicrobial resistance surveillance activities in Australia?

4. Does ACPM support the revised indications below:

Zevtera 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 published therapeutic guidelines on the appropriate use of antibacterial agents.

The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Advice sought from the ACPM

The ACPM has been requested to provide advice in regard to Zevtera on four specific issues. The applicant provides additional information in response to Issues 1 and 2 below.

The applicant does not wish to provide further comment in regard to Issues 3 or 4.

Issue 1

1. Does the ACPM consider that the data from Study BAP248/307 is sufficient to support the use of Zevtera for the treatment of HAP, excluding VAP (ventilator associated pneumonia)? Does ACPM consider that the comparator (ceftazidime+linezolid) used in this study is an appropriate comparator?

Applicant's response

Linezolid and ceftazidime were chosen as comparators for Study BAP248/307 because they are standard first line therapies for subjects with hospital-acquired pneumonia (HAP). Ceftazidime 2 g every 8 h is the most active cephalosporin towards susceptible non-fermenter Gram negative bacilli (comparable to ceftobiprole 500 mg every 8 h, compensating for a shorter $t_{1/2}$ with a higher dose and having similar minimum inhibitory concentration [MIC] distribution). The use of linezolid and ceftazidime as comparators at the planned study doses was consistent with the most recent recommendations from the American Thoracic Society (ATS), although the 2 h infusion time for ceftazidime was longer than is usual in clinical practice. This longer infusion time increases %T>MIC and thus potential antibacterial activity in the comparator arm.

Inclusion of linezolid in the comparator combination provided activity against MRSA that is lacking in ceftazidime; linezolid was considered to be superior to glycopeptides for the treatment of *S. aureus* pneumonia.

Issue 2

2. Does ACPM have concerns about the numerical imbalance in microbiological eradication rates (MER) with a lower percentage of subjects in the Zevtera group achieving microbiological eradication (Study BAP248/307)?

Applicant's response

1. Assessment of microbiological eradication

The microbiological outcome at the TOC visit in Study BAP248/307 was derived from a combination of clinical and microbiological assessment at baseline and at the TOC visit.

Given its timing (7 to 14 days after EOT), a microbiological sample for culture was often not available at TOC, particularly if subjects were cured or substantially improved, as respiratory samples are generally not obtained from cured patients. In accordance with the protocol definition, in the absence of a valid microbiological sample, microbiological outcome was 'presumed' based solely on the clinical outcome at the TOC visit.

For analyses of microbiological eradication rates, subjects were classified as having microbiological eradication irrespective of whether 'eradication' was 'confirmed' (no growth in a valid microbiological culture at TOC regardless of the clinical outcome) or 'presumed' (for subjects with clinical cure who had no valid microbiological sample at the TOC visit). Subjects with clinical failure who had no valid microbiological sample at the TOC visit were classified as microbiological failures due to 'presumed' persistence.

The majority (> 95%) of subjects who were classified as microbiological eradications in both groups were 'presumed' eradications. Efficacy by baseline pathogen may therefore be best described by clinical cure rates rather than microbiological eradication rates.

2. Microbiological outcomes

The overall microbiological eradication rate in the ceftobiprole group was 62.9% (73/116; 70 'presumed' and 3 'confirmed' eradications), compared to 67.5% (81/120; 78 'presumed' and 3 'confirmed' eradications) in the linezolid/ ceftazidime group.

However, in subjects with clinical cure, 73/86 (85%) in the ceftobiprole group and 81/94 (86%) in the linezolid/ceftazidime group, had an outcome of microbiological eradication (presumed plus confirmed). Of these subjects, 'confirmed' microbiological eradications were comparable between the treatment groups (3/73 in the ceftobiprole group and 3/81 in the linezolid/ceftazidime group).

Differences in microbiological eradication rates between the ceftobiprole and linezolid/ceftazidime treatment groups (60.3% versus 65.0%, respectively) were only observed in the subgroup of subjects with 'presumed' eradication. In contrast, microbiological outcome in subjects with a valid microbiological sample at the TOC visit was comparable between the ceftobiprole and linezolid/ceftazidime groups.

Valid microbiological samples were available at TOC for subjects with a clinical outcome of cure for 16/86 ceftobiprole subjects (18.6%) and 16/94 linezolid/ceftazidime subjects (17.0%). For subjects with a clinical outcome of failure, valid microbiological samples were available at TOC for 7/30 ceftobiprole subjects (23.3%) and 9/26 linezolid/ceftazidime subjects (34.6%).

The rate of 'confirmed' microbiological failure (persistence or colonization) in subjects with clinical cure was also comparable between the treatment groups. Microbiological failure in clinically cured subjects was observed in 13/86 subjects (15.1%) in the ceftobiprole group, and 13/94 subjects (13.8%) in the linezolid/ceftazidime group. No subjects in either treatment group with clinical failure at the TOC visit had 'confirmed' microbiological eradication. The rate of 'confirmed' microbiological failure (that is, persistence or superinfection) in subjects with clinical failure at TOC was higher in the linezolid/ceftazidime group: 7/30 subjects (23.3%) in the ceftobiprole group and 9/26 subjects (34.6%) in the linezolid/ceftazidime group.

3. Microbiological eradication and clinical cure by pathogen

Differences in clinical cure and eradication rates by pathogen between treatment groups, with a tendency towards higher cure and eradication rates in the comparator group were observed in the analyses of 'All subjects' (that is, 'VAP subjects' and 'HAP excluding VAP subjects' combined). However, for Gram positive pathogens and most of the Gram negative pathogens, these differences were driven by the inferior outcome of ceftobiprole in VAP subjects (see Table 15). For the larger group of HAP (excluding VAP) subjects, clinical cure

and microbiological eradication rates were similar, in particular for Gram positive pathogens but also for most of the Gram negative pathogens.

Clinical cure and microbiological eradication for infections with Gram-negative pathogens are summarised in Table 15 and are discussed in more detail below:

- For the relatively small sample of *Haemophilus* and *Acinetobacter* species at baseline, numerically lower clinical cure and microbiological eradication rates were observed, in both the VAP and HAP (excluding VAP) subgroups.
- For the most prevalent *Enterobacteriaceae*, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp.* and *Proteus mirabilis*, and for *Pseudomonas aeruginosa*, clinical cure and microbiological eradication rates were similar between treatment groups in HAP (excluding VAP) subjects. For *K. pneumoniae*, *Enterobacter spp.* *P. mirabilis* and *P. aeruginosa*, there was a tendency towards higher clinical cure and microbiological eradication rates in the ceftobiprole group.
- When members of the family of *Enterobacteriaceae* were combined and analysed as a group, a disparity between the clinical cure rate and the microbiological eradication rate was observed in both the VAP and HAP (excluding VAP) ceftobiprole groups. In HAP (excluding VAP) subjects, the clinical cure rates were similar for ceftobiprole (72%) and comparator (71%), but microbiological eradication was lower for ceftobiprole: (63%, [29/46] versus 71%, [32/45]). This difference is explained by 4 of the 33 clinically cured ceftobiprole subjects who had confirmed microbiological persistence, which was not confined to any specific species but was observed for single cases of *P. mirabilis*, *S. marcescens*, *Enterobacter cloacae* and *K. pneumoniae*.

Conclusions

Clinical and microbiological outcomes were comparable and consistent between treatment groups for Gram positive pathogens, *P. aeruginosa*, and the most prevalent *Enterobacteriaceae* species (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp.* and *Proteus mirabilis*).

Only in the relatively small sample of *Acinetobacter baumannii* and *Haemophilus* species, numerically lower clinical cure and microbiological eradication rates were observed in the ceftobiprole group.

For the overall group of *Enterobacteriaceae*, the lower microbiological eradication rate or ceftobiprole despite similar clinical cure rates was explained by single cases of 4 clinically cured subjects with microbiological persistence of *P. mirabilis*, *S. marcescens*, *Enterobacter cloacae* and *K. pneumoniae*. Since persistent *Enterobacteriaceae* were not observed in subjects with clinical failure in the ceftobiprole group, the clinical relevance of this microbiological persistence in clinically cured subjects is open to question.

Non-inferiority of ceftobiprole to linezolid/ceftazidime for clinical cure rates at the TOC visit was demonstrated in the overall study population and in the large group of HAP subjects (excluding VAP). The lower bounds of the 95% CIs of the between-group difference were -7.3% (ITT analysis set) and -6.9% (CE analysis set), and were therefore well within the pre-specified non-inferiority margin of 15%.

Table 15: Study BAP248/307: Clinical cure and microbiological eradication by pathogen (Microbiologically Evaluable analysis set)

Pathogen	HAP (excluding VAP)		VAP		All subjects	
	Ceftobiprole	Linezolid/ ceftazidime	Ceftobiprole	Linezolid/ ceftazidime	Ceftobiprole	Linezolid/ ceftazidime
	N=116 n (%)	N=120 n (%)	N=46 n (%)	N=50 n (%)	N=162 n (%)	N=170 n (%)
<i>S. aureus</i>	39	49	25	28	64	77
Clinical cure	28 (72)	36 (73)	9 (36)	16 (57)	37 (58)	52 (68)
M. eradication	23 (59)	31 (63)	10 (40)	18 (64)	33 (52)	49 (64)
MSSA	20	30	17	19	37	49
Clinical cure	15 (75)	24 (80)	5 (29)	10 (53)	20 (54)	34 (69)
M. eradication	15 (75)	21 (70)	5 (29)	12 (63)	20 (54)	33 (67)
MRSA	19	19	8	9	27	28
Clinical cure	13 (68)	12 (63)	4 (50)	6 (67)	17 (63)	18 (64)
M. eradication	8 (42)	10 (53)	5 (63)	6 (67)	13 (48)	16 (57)
<i>S. pneumoniae</i>	7	14	4	1	11	15
Clinical cure	7 (100)	13 (93)	0 (0)	1 (100)	7 (64)	14 (93)
M. eradication	7 (100)	13 (93)	0 (0)	1 (100)	7 (64)	14 (93)
Enterobacteriaceae	46 ¹	45 ²	18	16	64	61
Clinical cure	33 (72)	32 (71)	5 (28)	6 (38)	38 (59)	38 (62)
M. eradication	29 (63)	32 (71)	6 (33)	7 (44)	35 (55)	39 (64)
<i>E. coli</i>	14	11	6	3	20	14
Clinical cure	8 (57)	7 (64)	2 (33)	1 (33)	10 (50)	8 (57)
M. eradication	8 (57)	7 (64)	2 (33)	1 (33)	10 (50)	8 (57)
<i>K. pneumoniae</i>	12	19	4	4	16	23
Clinical cure	11 (92)	15 (79)	0 (0)	1 (25)	11 (69)	16 (70)
M. eradication	10 (83)	15 (79)	0 (0)	1 (25)	10 (63)	16 (70)
<i>Enterobacter spp.</i>	9	7	3	2	12	9
Clinical cure	7 (78)	3 (43)	1 (33)	0 (0)	8 (75)	3 (33)
M. eradication	6 (67)	3 (43)	2 (66)	0 (0)	8 (75)	3 (33)
<i>Proteus spp.</i>	5	5	2	5	7	10
Clinical cure	4 (80)	2 (40)	0 (0)	1 (20)	4 (57)	3 (30)
M. eradication	3 (60)	2 (40)	0 (0)	2 (40)	3 (43)	4 (40)
<i>Serratia spp.</i>	5	4	3	3	8	7
Clinical cure	3 (60)	2 (50)	1 (33)	3 (100)	4 (50)	5 (71)
M. eradication	2 (40)	2 (50)	1 (33)	3 (100)	3 (38)	5 (71)
<i>P. aeruginosa</i>	16	20	11	14	27	34
Clinical cure	12 (75)	14 (70)	5 (45)	10 (71)	17 (63)	24 (71)
M. eradication	9 (56)	11 (55)	4 (36)	8 (57)	13 (48)	19 (56)
<i>A. baumannii</i>	8	12	6	5	14	17
Clinical cure	4 (50)	9 (75)	3 (50)	4 (80)	7 (50)	13 (77)
M. eradication	4 (50)	9 (75)	3 (50)	3 (60)	7 (50)	12 (71)
<i>Haemophilus</i>	5	9	4	0	9	9
Clinical cure	2 (40)	9 (100)	1 (25)	na	3 (33)	9 (100)
M. eradication	2 (40)	9 (100)	1 (25)	na	3 (33)	9 (100)

Numbers in bold refer to the number of subjects with a pathogen in the respective group.

n = number of subjects with an outcome of clinical cure or eradication for the respective pathogen at TOC.

¹ 46 subjects with Enterobacteriaceae isolated at baseline, including: *E. coli* (monomicrobial); n=11, *E. coli* plus *Klebsiella spp.*; n=1, *E.*

Pathogen	HAP (excluding VAP)		VAP		All subjects	
	Ceftobiprole	Linezolid/ ceftazidime	Ceftobiprole	Linezolid/ ceftazidime	Ceftobiprole	Linezolid/ ceftazidime
	N=116 n (%)	N=120 n (%)	N=46 n (%)	N=50 n (%)	N=162 n (%)	N=170 n (%)

coli plus *Proteus spp.*; n=1, *E. coli* plus *Providencia spp.*; n=1, *K. pneumoniae* (monomicrobial); n=9, *Klebsiella oxytoca*; n=1, *K. pneumoniae* plus *Proteus spp.*; n=1, *K. pneumoniae* plus *Serratia spp.*; n=1, *K. pneumoniae* plus *Enterobacter spp.*; n=1, *Enterobacter spp.*; n=8, *Serratia spp.*; n=5, *Proteus mirabilis*; n=3, *Citrobacter spp.*; n=2, *Providencia spp.*; n=1.

² 45 subjects with Enterobacteriaceae isolated at baseline, including: *E. coli* (monomicrobial); n=8, *E. coli* plus *K. pneumoniae*; n=1, *E. coli* plus *Proteus spp.*; n=1, *E. coli* plus *K. pneumoniae* plus *Serratia spp.*; n=1, *K. pneumoniae* (monomicrobial); n=14, *Klebsiella oxytoca*; n=1, *Klebsiella spp.*; n=2, *K. pneumoniae* plus *Proteus spp.*; n=2, *K. pneumoniae* plus *Proteus spp.* plus *Serratia spp.*; n=1, *Enterobacter spp.*; n=7, *Serratia spp.*; n=2, *Proteus mirabilis*; n=3, *Citrobacter spp.*; n=1, *Hafnia alvei*; n=1.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Zevtera powder for injection containing 667 mg of ceftobiprole medocaril (as sodium) (500 mg ceftobiprole) to have an overall positive benefit–risk profile for the amended indication;

Zevtera is indicated for the treatment of the following infections in adults suspected or proven to be caused by designated susceptible microorganisms:

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

Consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the ACPM consider that the data from Study BAP248/307 is sufficient to support the use of Zevtera for the treatment of HAP, excluding VAP (ventilator-associated pneumonia)? Does ACPM consider that the comparator (ceftazidime+linezolid) used in this study is an appropriate comparator?*

The ACPM considered the data submitted were not particularly robust and only provided limited support for efficacy in a subset of HAP/without VAP population. The ACPM observed that the evidence came from a single study, and considered it demonstrated marked inferiority in a key subgroup (VAP) and key outcome (microbiological eradication).

Although the comparator is not a recommended standard comparator recommended in Australia it was considered adequate for the purpose.

2. *Does ACPM have concerns about the numerical imbalance in microbiological eradication rates (MER) with a lower percentage of subjects in the Zevtera group achieving microbiological eradication (Study BAP248/307)?*

The numerical imbalance in microbiological eradication rates (MER) were of concern to the ACPM; however this concern was mitigated if the VAP sub population exclusion is accepted. Eradication in the ME group was 53.7% (87/162) for ceftobiprole, and 62.4% (106/170) for the comparator. Then again, these results are driven by the VAP subgroup where MER was reported as 30.4% (14/46) for the ceftobiprole group and 50.0% (25/50) for the comparator. By excluding the VAP subgroup, eradication was 63% versus 68%.

3. *What is the view of the ACPM with regards to the potential risk of developing antibiotics resistance to Zevtera? Does ACPM have any specific recommendation with regards to the antimicrobial resistance surveillance activities in Australia?*

The ACPM advised that resistance is a real risk and it is a serious public health matter. This antibiotic needs to be effective in the longer term. Use is likely to be low initially so there would be a low risk of resistance, but resistance risk will increase over time.

Stewardship is vital to maintain efficacy of antibacterial products and the ACPM advised surveillance should be integrated into national surveillance activities where possible – either through AGAR or the developing national antimicrobial resistance surveillance programme being developed by the ACSQHC.

4. *Does ACPM support the revised indications below:*

Zevtera 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 published therapeutic guidelines on the appropriate use of antibacterial agents.

The ACPM advised that the indication should reinforce the need for restricted use of innovator reserve antibiotics to susceptible bacteria, keeping in mind the need for stewardship in the name of individual and public health. The ACPM advised the use of the indication statement above.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zevtera ceftobiprole medocaril sodium 667 mg powder for injection in a 20 mL vial, indicated for:

Zevtera (ceftobiprole medocaril sodium) is indicated for the treatment of the following infections in adults suspected or proven to be caused by designated susceptible microorganisms:

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

Specific conditions of registration applying to these goods

The Zevtera (ceftobiprole medocaril sodium) Risk Management Plan (RMP), *Implement EU-RMP version 4.0 dated 21 July 2015 (data lock point 31 March 2015) with Australian Specific Annex version 2.0 dated 21 August 2015*, included with submission PM-2014-03155-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Zevtera at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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