EU RISK MANAGEMENT PLAN (EU – RMP)

CEFTOBIPROLE 500 mg powder for concentrate for solution for infusion (ZEVTERA and associated names)

PRODUCT DETAILS

Invented name of the medicinal product (product short name):	ZEVTERA
Active substance(s) (INN or common name):	Ceftobiprole (as ceftobiprole medocaril)
Pharmaco-therapeutic group (ATC Code):	Other cephalosporins (J01DI01)
Medicinal Product Code (from EudraVigilance):	PRD 988056 (UK)
Authorisation procedure(s) (central, mutual recognition, decentralised, national):	Decentralised
Name of Marketing Authorisation Holder or Applicant:	Basilea Medical Ltd (c/o Cox Costello & Horne Limited) Langwood House 63–81 High Street Rickmansworth Hertfordshire WD3 1EQ United Kingom
Date and country of first authorisation worldwide:	Canada (26 June 2008) – indication for use: complicated skin and skin structure infections (cSSSI)
Date and country of first launch worldwide:	Canada (August 2008)
Date and country of first authorisation in the EEA:	UK (20 Nov 2013)
Date and country of first launch in the EEA:	30 September 2014, Germany

Data lock point for EU – RMP | 31/03/2015 | Version | 4.0

Brief description of product (chemical class, mode of action etc)	Ceftobiprole medocaril (BAL5788) is the water-soluble prodrug of ceftobiprole (BAL9141), a novel cephalosporin for intravenous administration. It is a beta-lactam antibiotic with bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), *Enterobacteriaceae*, and *Pseudomonas aeruginosa*. Ceftobiprole binds tightly to the penicillin-binding proteins (PBPs) related to beta-lactam resistance in staphylococci (PBP2a) and pneumococci (PBP2x).
Indications:	Ceftobiprole is indicated for the treatment of nosocomial pneumonia (NP) and community-acquired pneumonia (CAP) – excluding ventilator-associated pneumonia (VAP) – in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Dosage:	The recommended dose is 500 mg ceftobiprole administered as a 2-hour intravenous infusion every 8 hours for infections documented or suspected to be due to Gram-positive, Gram-negative, or both Gram-positive and Gram-negative bacteria. The usual treatment duration is 4–14 days for CAP and 7–14 days for NP depending on the disease severity, and the patient's clinical response.
Pharmaceutical forms(s) and strength(s)	Each vial contains 500 mg of ceftobiprole (as 666.7 mg of ceftobiprole medocaril) in the form of white, yellowish to slightly brownish, cake to broken cake or powder for concentrate for solution for infusion. After reconstitution, each mL of concentrate contains 50 mg of ceftobiprole (as 66.7 mg of ceftobiprole medocaril).

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INTRODUCTION

This Risk Management Plan has been prepared to support the Marketing Authorisation (MA) for ceftobiprole for use in the indications of Community-Acquired Pneumonia (CAP) and Nosocomial Pneumonia (NP). Ceftobiprole medocaril (BAL5788) is the water-soluble prodrug of a novel cephalosporin, ceftobiprole, which has been developed for intravenous administration.

Ceftobiprole is a novel cephalosporin, characterised by potent, broad-spectrum antimicrobial activity. It provides a unique spectrum of activity against both Gram-positive and Gram-negative respiratory tract pathogens, including those that have developed various forms of antibiotic resistance. Combined with a low potential for drug interactions and a clinically good and tolerable safety profile, it provides an additional alternative to physicians dealing with serious, difficult to treat pulmonary infections in hospitalized subjects.

With regard to the pneumonia indications, the safety and efficacy of ceftobiprole has been established in two double-blind randomised, multicentre, comparator-controlled Phase 3 studies in hospitalised subjects. These studies form the basis of the Phase 3 data package, which supports this MAA and provides information to determine those risks considered as either as identified or as potential safety risks for this product.

Ceftobiprole was also previously evaluated in clinical studies of complicated skin and skin structure infections (cSSSIs).

SUMMARY OF THE EU RISK MANAGEMENT PLAN

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Identified risks	
Hepatic enzymes increased	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC (section 4.8) as an Undesirable effect.
Hyponatraemia	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC (section 4.8) as an Undesirable effect.
Anaphylactic reactions	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as a warning in the special warnings and precautions section (4.4).
Hypersensitivity reactions	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as a contraindication for use in subjects with known hypersensitivity reactions to cephalosporins /beta-lactams (section 4.3).
Pseudomembranous colitis / *Clostridium difficile* colitis	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as a warning in the special warnings and precautions section (4.4).
Injection/infusion-site reactions	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC (section 4.8) as an Undesirable effect.
Localised fungal infections	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC (section 4.8) as an Undesirable effect.
Convulsions	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC (section 4.8) as an Undesirable effect and also included as a warning in section 4.4.
Renal toxicity (including potential interaction with nephrotoxic drugs)	Routine pharmacovigilance and ongoing risk/benefit evaluation Targeted follow-up questionnaire with discussion in Periodic Safety Update Reports (PSURs).	Included in SmPC as a warning in the special warnings and precautions section (4.4).
Precipitation of infusion solutions when mixed with calcium-containing solutions	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as a warning in section 4.4.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Potential risks	
Development of drug-resistant bacteria.	Routine pharmacovigilance and ongoing risk/benefit evaluation. Targeted follow-up questionnaire for lack of effect with discussion in PSURs. Monitoring of ceftobiprole's activity against clinically relevant pathogens through *in vitro* surveillance studies of clinical isolates at geographically distributed sites, including multiple sites in various European countries.	Information on the potential for the development of drug resistant strains is included in SmPC (sections 4.1 and 5.1).
Off-label use in adults and children	Routine pharmacovigilance and ongoing risk/benefit evaluation. Targeted follow-up questionnaire for lack of efficacy with discussion in PSUR. Will be captured in a Post-authorization Safety Study (PASS).	In the SmPC it is stated that ceftobiprole treatment should not be initiated in patients with ventilator-associated pneumonia (4.4), and ceftobiprole is not recommended for use in patients aged < 18 years (4.2).
Haemolytic anaemia/ positive Coombs test	Routine pharmacovigilance and ongoing risk/benefit evaluation. Targeted follow-up questionnaire with discussion in PSURs. Inclusion of the Coombs test, haptoglobin, and reticulocyte testing, in future clinical study/ies.	In section 4.4 of the SmPC the prescriber is informed that direct antiglobulin test seroconversion may occur. patients experiencing anaemia during or after treatment with ceftobiprole should be investigated for haemolytic anaemia.
Interaction with copper reduction technique to measure urine glucose	Routine pharmacovigilance and ongoing risk/benefit evaluation. Targeted follow-up questionnaire with discussion in PSURs.	Included in the SmPC to advise physicians that ceftobiprole may interfere with tests using the copper reduction technique, and recommend the use of enzyme-based methods to detect glucosuria (4.5).
Interaction with Jaffé method to measure creatinine.	Routine pharmacovigilance and ongoing risk/benefit evaluation. Targeted follow-up questionnaire with discussion in PSURs.	Included in the SmPC that it is not known whether ceftobiprole interferes with the Jaffé reaction and that during treatment with ceftobiprole it is recommended that an enzymatic method of measuring serum creatinine be used (4.5).
Interaction with drugs transported via OATP1B1 and OATP1B3	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as an interaction in section 4.5
CYP drug interactions.	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Included in SmPC as a potential interaction in section 4.5

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Missing information	
Pregnancy and lactation	Routine pharmacovigilance and ongoing risk/benefit evaluation.	Specific wording is in the warnings and precautions section (4.6) providing information about the lack of data in this population and therefore any usage should be based upon risk/benefit assessment.
Paediatric use	Routine pharmacovigilance and ongoing risk/benefit evaluation. Studies per approved PIP.	No specific risk minimisation activities. Keep under close review and identify any relevant reports in PSURs.
Safety data in patients with end stage renal failure	Routine pharmacovigilance and ongoing risk/benefit evaluation. Conduct of a PASS.	Included in the SmPC that, ceftobiprole is to be used with caution in patients with severe renal impairment with a dosing recommendation for patients with end-stage renal disease.
Use in patients with hepatic impairment	Routine pharmacovigilance and ongoing risk/benefit evaluation. Conduct of a PASS.	Included in the SmPC that there is no experience in patients with hepatic impairment and that, because ceftobiprole undergoes minimal hepatic metabolism, no dosage adjustment is needed in patients with hepatic impairment (4.2).
Use in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppresion	Routine pharmacovigilance and ongoing risk/benefit evaluation. Conduct of a PASS.	Included in the SmPC that there is no experience with ceftobiprole in this population and recommends caution when treating such patients (4.4).