



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for ceftaroline fosamil

Proprietary Product Name: Zinfofo

Sponsor: AstraZeneca Pty Ltd

May 2013

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 Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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.

Copyright

© Commonwealth of Australia 2013

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

I. Introduction to product submission	4
Submission details	4
Product background	4
Regulatory status	5
Product Information	5
II. Quality findings	8
Drug substance (active ingredient)	8
Drug product	8
Advisory committee considerations	9
Quality summary and conclusions	9
III. Nonclinical findings	10
Introduction	10
Pharmacology	10
Pharmacokinetics	12
Toxicology	13
Nonclinical summary and conclusions	18
IV. Clinical findings	20
Introduction	20
Pharmacokinetics	21
Pharmacodynamics	22
Efficacy	22
Safety	24
Clinical summary and conclusions	26
V. Pharmacovigilance findings	27
Risk management plan	27
VI. Overall conclusion and risk/benefit assessment	35
Quality	35
Nonclinical	35
Clinical	36
Risk management plan	46
Risk-benefit analysis	46
Outcome	51
Attachment 1. Product Information	51
Attachment 2. Extract from the Clinical Evaluation Report	51

I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	7 February 2013
<i>Active ingredient:</i>	ceftaroline fosamil
<i>Product Name:</i>	Zinforo
<i>Sponsor's Name and Address:</i>	AstraZeneca Pty Ltd 5 Alma Road North Ryde NSW 2113
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	600 mg
<i>Container:</i>	Glass vial
<i>Pack size:</i>	10 vials per carton
<i>Approved Therapeutic use:</i>	<i>Zinforo is indicated for the treatment of patients with the following infections proven or strongly suspected to be caused by designated susceptible bacteria:</i> <ul style="list-style-type: none">• <i>Complicated skin and soft tissue infections</i>• <i>Community-acquired pneumonia</i>
<i>Route of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	Adults: 600 mg every 12 hours by intravenous (IV) infusion over 60 minutes for 5-7 days for community acquired pneumonia (CAP) or 5-14 days for complicated skin and soft tissue infections (cSSTI). Dose reductions are proposed for patients with renal impairment.
<i>ARTG Number:</i>	192260

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd to register a new chemical entity, ceftaroline fosamil (Zinforo), for the treatment of adults with complicated skin and soft tissue infection (cSSTI) or community-acquired pneumonia (CAP). The proposed indications were:

Zinforo is indicated for the empirical and directed treatment of patients with the following infections:

- *Complicated skin and soft tissue infections*
- *Community-acquired pneumonia*
- Ceftaroline fosamil is an N-phosphono-type prodrug of ceftaroline (a cephalosporin antibiotic) and is administered by infusion. The proposed treatment regimen is 600 mg every 12 h by 60-min IV infusion, for 5-7 (CAP) or 5-14 days (cSSTI), in patients 18 years and older.
- Ceftaroline fosamil is a semi-synthetic pro-drug from the cephalosporin class of β -lactam antibiotics. Ceftaroline fosamil is converted to the active ceftaroline in plasma by a phosphatase enzyme. Ceftaroline is bactericidal *in vitro* due to inhibition of bacterial cell wall synthesis by binding to penicillin binding proteins (PBPs).
- Ceftaroline is stated to be active against bacteria that produce classical Class A β -lactamases such as TEM-1, TEM-2 or SHV-1. However, ceftaroline is not active against Gram-negative bacteria producing extended spectrum β -lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), Class B metallo- β -lactamases or Class C (AmpC cephalosporinases). One or more of these mechanisms may co-exist in the same bacterium. Unlike other cephalosporins, ceftaroline is stated to be active against the altered PBPs found in methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) that result in resistance to these other antibiotics. There is no cross resistance between ceftaroline and any non- β -lactam antibiotics.

Regulatory status

Table 1 provides a list of major countries in which a similar application had been submitted and/or approved as of November 2012.

Table 1. Submission and approval status of Zinfofo vials

Country	Submission date	Approval date	Approved indication
European Union*	15 Dec 2010	23 Aug 2012	Zinfofo is indication in adults for the treatment of the following infections (see sections 4.4 and 5.1): <ul style="list-style-type: none"> • Complicated skin and soft tissue infections (cSSTI) • Community-acquired pneumonia (CAP) Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Switzerland	20 Dec 2011		Evaluation still ongoing
United States**	29 Dec 2009	29 Oct 2010	Teflaro™ is a cephalosporin antibacterial indicated for the treatment of the following infections caused by designated susceptible bacteria: <ul style="list-style-type: none"> • Acute bacterial skin and skin structure infections (ABSSSI) • Community-acquired bacterial pneumonia (CABP)

* Centralised Procedure - Rapporteur (United Kingdom) and co-rapporteur (Estonia)
 ** Forest Laboratories responsible in these markets

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

List of abbreviations used in this AusPAR

AE	adverse event
Ae	amount of unchanged drug excreted into the urine
Ae _{0-t}	cumulative amount of unchanged drug excreted into the urine from time 0 to time t
APTT	activated partial thromboplastin time
AUC _{0-t}	area under the plasma concentration versus time curve from time zero to time t
AUC _{0-∞}	area under the plasma concentration versus time curve from time zero to infinity
CAP	community acquired pneumonia
CABP	community acquired bacterial pneumonia
CE	clinically evaluable
CI	confidence interval
CL	plasma clearance
CL _r	renal clearance
C _{max}	maximum plasma drug concentration
cMITT	clinical modified intention to treat
CrCl	creatinine clearance
cSSTI	complicated skin and soft tissue infections
CT	computerised tomography
CXR	chest X-ray
Bias PE%	Calculated as the population mean predicted exposure measure minus the individual predicted exposure measure multiplied by 100 and then divided by the individual predicted exposure measure
DAE	discontinuation due to adverse event
DM	diabetes mellitus
ECG	electrocardiogram
EOT	end of treatment
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease
IM	intramuscular
IV	intravenous
IVRS	interactive voice response system
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LFU	late follow-up
ME	microbiologically evaluable

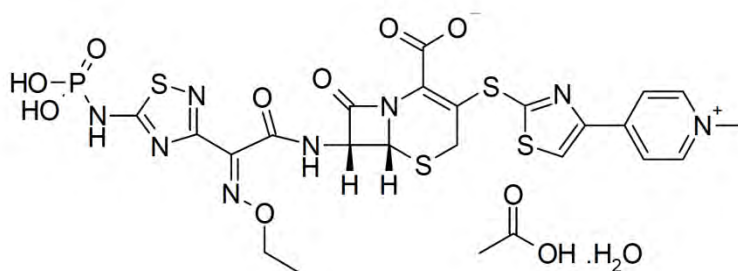
MIC	minimal inhibitory concentration
MIC ₉₀	minimal inhibitory concentration required to inhibit the growth of 90% of organisms
MITT	modified intention to treat
MITTE	modified intention to treat efficacy
mMITT	microbiological modified intention to treat
mMITTE	microbiological modified intention to treat efficacy
MW	Molecular weight
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	methicillin susceptible <i>Staphylococcus aureus</i>
PBP	penicillin binding protein
PCS	potentially clinically significant
PD	pharmacodynamic
PE	predicted exposure
PK	pharmacokinetic
Precision PE%	Calculated as the absolute value of the PE%
PNSP	penicillin non-susceptible <i>Streptococcus pneumoniae</i>
PRP	Penicillinase-resistant penicillin
PRSP	penicillin resistant <i>Streptococcus pneumoniae</i>
PSSP	penicillin susceptible <i>Streptococcus pneumoniae</i>
PT	Prothrombin time
PTA	probability of target attainment
PVD	peripheral vascular disease
QTcIb	QT interval corrected for heart rate using an individual subject correction formula based on the baseline QT-RR slope
q12h	twelve hourly intervals
SAE	serious adverse event
Std	Standard
TEAE	treatment emergent adverse event
t _½	terminal elimination half-life
T _{max}	time of maximum plasma drug concentration
TOC	test of cure
v	Volume
VISA	vancomycin intermediate <i>Staphylococcus aureus</i>
VRSA	vancomycin resistant <i>Staphylococcus aureus</i>

II. Quality findings

Drug substance (active ingredient)

Ceftaroline fosamil is a semisynthetic prodrug of ceftaroline, a new cephalosporin antibiotic. The prodrug has been developed because the aqueous solubility of ceftaroline is insufficient for parenteral delivery at the doses required. Ceftaroline fosamil is obtained as the monoacetate monohydrate solvate. The structure described in Figure 1. The drug substance is sterilised by filtration and isolated by crystallisation.

Figure 1. Chemical structure



The two chiral centres in the molecule have *R* configuration and the oxime has *Z* configuration.

The therapeutically active moiety, ceftaroline, is the free amine produced by hydrolysis of the phosphonoamino group.

The drug substance, ceftaroline fosamil monoacetate monohydrate, is a crystalline solid that has no known polymorphs. It is manufactured from a common, readily available, fermented cephalosporin starting material, which is subjected to seven synthetic steps to produce the drug substance.

Nine identified impurities are controlled in the drug substance specifications. The limits for five of those impurities exceed the International Conference on Harmonization (ICH) qualification threshold and have been referred to the Medicines Toxicology Evaluation Section at the TGA.

Drug product

Zinforo powder for injection is a sterile, pyrogen-free powder blend containing ceftaroline fosamil monoacetate monohydrate 668.4 mg, equivalent to ceftaroline fosamil 600 mg, and L-arginine 395 mg (alkalising agent). The two sterile powders are aseptically blended, then vials are aseptically filled. Vials are single use. Zinforo vials are constituted with sterile water for injections prior to preparation of a dilute infusion solution. The product contains no antimicrobial preservative.

Six degradants are controlled in the finished product specifications. One of these is ceftaroline, the therapeutically active moiety. Another is an 'arginine adduct'. The limits for all specified degradants exceed the ICH qualification threshold and have been referred to the Medicines Toxicology Evaluation Section at the TGA.

Significant degradation of the active ingredient occurs during storage of Zinforo powder for injection. However, provided the limits proposed for degradants are accepted by the Medicines Toxicology Evaluation Section at the TGA, the proposed shelf life of 2 years below 25°C is acceptable.

Endotoxin and sterility aspects of the submission have been cleared.

As the product, once constituted, is a simple aqueous solution for intravenous infusion, no bioavailability data were submitted.

Advisory committee considerations

This submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee for Prescription Medicines (ACPM) at its 146th meeting on 23 July 2012.

PSC consideration

The Pharmaceutical Subcommittee of the ACPM recommended that the company be asked to provide some additional data. The following information has been provided.

1. Batch analysis data were provided for three recent consecutive validation batches of the API. These batches complied fully with the proposed specifications.
2. The company stated that future stability studies will be conducted in accordance with GMP requirements.
3. Batch analysis data were provided for three recent consecutive batches of the finished product. These batches complied fully with the proposed specifications.

The applicant has since provided responses to questions raised by the TGA evaluator and additional matters raised by the subcommittee.

Quality summary and conclusions

There are now no objections in respect of Chemistry, Manufacturing and Controls to registration of Zinforo powder for injection subject to resolution of the following matters.

1. The limits proposed for related substances and degradants in the active pharmaceutical ingredient (API) and finished product specifications require clearance by the Medicines Toxicology Evaluation Section.
2. The product information document submitted with the company's response dated 27 August 2012 is satisfactory in respect of Chemistry, Manufacturing and Controls except for the second paragraph under the heading *Description*. Amendments to this PI section were recommended but these are beyond the scope of this AusPAR.
3. An updated Good Manufacturing Practice (GMP) clearance letter should be submitted for one site, as the current clearance will expire in January 2013.

The Office of Manufacturing Quality has advised that the GMP clearance letter issued for another site covers manufacture of sterile ceftaroline fosamil, but does not cover manufacture of sterile arginine, manufacture of the sterile bulk blend or quality control (QC) testing of the bulk blend. The company should submit an appropriate GMP clearance letter for this site.

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

The sponsor has presented a high quality, comprehensive dossier of experiments performed by reliable laboratories. The crucial toxicological studies were performed to Good Laboratory Practice (GLP) standard.

Pharmacology

Primary pharmacology

Ceftaroline fosamil is an *N*-phosphono-type prodrug of the cephalosporin antibiotic ceftaroline. As is typical of β -lactam-type drugs, ceftaroline binds to PBPs and inhibits the last step in bacterial cell wall biosynthesis.

Bacteria can develop significant resistance to β -lactam antibiotics by several mechanisms, including: acquisition of a new PBP with low binding affinity for β -lactam antibiotics (for example, PBP2a of MRSA); decreasing the β -lactam antibiotic binding affinity of an endogenous PBP via gene mutation (for example, PBP2x of penicillin-resistant *Streptococcus pneumoniae*); and secretion of β -lactamase into the periplasmic space to inactivate the antibiotic before it interacts with PBPs. The continuing emergence of antibiotic-resistant bacterial strains has become an important public health issue. Accordingly, ceftaroline's bactericidal activity towards antibiotic-resistant strains was a central focus of the sponsor's studies.

Ceftaroline was shown to bind to most PBPs from *Staphylococcus aureus* and *Streptococcus pneumoniae* strains, with an affinity comparable to or higher than comparator antibiotics. Notably, ceftaroline showed a high *in vitro* binding affinity for both PBP2a (most other β -lactams, with the exception of ceftobiprole, bind poorly to this protein) and PBP2x that was correlated with its low minimum inhibitory concentration (MIC) for bacterial strains expressing these proteins. *In vitro* studies using class A and C β -lactamases suggested that ceftaroline is less susceptible to β -lactamase hydrolysis than benzylpenicillin but is much less stable than cefepime. However, ceftaroline was shown to be a weak inducer of AmpC-type β -lactamases (class C) in various bacterial species.

The propensity for the development of ceftaroline resistance in strains of *Staphylococcus aureus* (both MRSA and MSSA), *Enterococcus faecalis* (both vancomycin-sensitive and -resistant), *Streptococcus pneumoniae* (both PRSP and PSSP), *Haemophilus influenzae*, and *Moraxella catarrhalis*, under conditions of *in vitro* exposure, was shown to be very low (of the order of 10^{-10} to 10^{-11}). Similarly, ceftaroline-resistant mutants were not detected following treatment of MRSA-induced osteomyelitis in rabbits with a sub-MIC dose of ceftaroline for two weeks. In contrast, ceftaroline-resistant mutants were readily selected from AmpC-inducible *Enterobacter cloacae* strains. The selected strains had a phenotype typical of AmpC-derepressed mutants. Hence, Enterobacteriaceae may not be an appropriate target for ceftaroline therapy.

The postantibiotic effect of ceftaroline (a measure of the rapidity of resumption of bacterial growth after antibiotic exposure) was determined *in vitro* for various bacterial species (both Gram-positive and -negative). Consistent with results for other β -lactam-type antibiotics, ceftaroline showed only a modest postantibiotic effect (ranged from 0-2.2 h after a 1 h incubation at 10 x MIC).

Ceftaroline offers the possibility of synergistic effects with other antibiotics. Combination with tobramycin (both at 0.5 x MIC) produced synergistic killing of two vancomycin-susceptible MRSA strains whilst the combination with amikacin produced synergistic killing of various bacterial strains. Antagonism was not observed when ceftaroline was combined with any of a variety of antibiotics.

A range of studies was presented that examined the bactericidal activity of ceftaroline towards Gram-negative and -positive bacteria, under both *in vitro* and *in vivo* conditions, and compared this activity with antibiotics that are currently in clinical use. These studies included the bacterial species and strains that are frequently implicated in the proposed clinical indications for ceftaroline therapy: complicated skin and soft tissue infection (most common pathogen is MRSA) and community-acquired pneumonia (many pathogens implicated, but *Haemophilus influenzae* and *Streptococcus pneumoniae* are common causes). For example, a Detroit study compared the *in vitro* bactericidal activity of ceftaroline, vancomycin, daptomycin, clindamycin, linezolid, sulfamethoxazole/trimethoprim, and ceftriaxone towards 132 strains of community-associated MRSA (including 17 DNSSA strains, 23 VISA strains, and 10 VRSA strains). It showed that ceftaroline was active against all strains (MICs were $\leq 1 \mu\text{g/mL}$) and had superior activity to the other antibiotics against VISA, VRSA, and DNSSA strains. Data on the activity of ceftaroline towards Australian isolates of bacterial pathogens were also provided by the sponsor.

Ceftaroline was used to treat septicemia in mice caused by both Gram-positive (various MRSA strains, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*) and -negative (*Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*) bacteria, and was shown to generally have similar or superior effectiveness to comparator drugs. MRSA-induced pneumonia and thigh muscle infections in mice were both shown to be more effectively treated with ceftaroline than with vancomycin. Likewise, ceftaroline showed similar or greater effectiveness than linezolid and vancomycin in treating MRSA- and *Enterococcus faecalis*-associated endocarditis and MRSA-associated osteomyelitis in rabbits. Furthermore, ceftaroline was shown to be effective in treating rabbit pneumonia induced by penicillin-sensitive, -intermediate, or -resistant *Streptococcus pneumoniae* strains.

Secondary pharmacodynamics and safety pharmacology

Ceftaroline and ceftaroline fosamil were tested for possible pharmacological activity towards a large panel of molecular targets including enzymes, receptors, transporters and ion channels. The only targets showing significant responses were the human Cav1.2 voltage-gated cardiac ion channel, which was inhibited by 30% at 68 $\mu\text{g/mL}$ of ceftaroline fosamil, and the hERG-encoded ion channel whose tail current density was weakly inhibited above ceftaroline fosamil concentrations of 600 $\mu\text{g/mL}$. Such concentrations are well beyond the expected clinical plasma levels: mean C_{max} for ceftaroline fosamil in humans following IV administration of 600 mg of ceftaroline fosamil was 2.0 $\mu\text{g/mL}$ (Clinical Study P903-13).

Specialised safety pharmacology studies examined test article effects on the central nervous, cardiovascular, respiratory and renal systems.

Ceftaroline fosamil, at IV doses up to 479 mg/kg, had no overt effects on rat physiological or behavioural parameters, although at 2,000 mg/kg it could induce tonic convulsion. The high dose at which ceftaroline fosamil induced convulsions makes it uncertain whether this is a significant risk for human use (discussed further below). At IV doses of 200 mg/kg and greater (but not at 100 mg/kg), ceftaroline fosamil significantly decreased the time of onset of pentylenetetrazole-induced seizure in rats. Again, the practical significance of this finding is uncertain because of the high doses employed. Administration of IV ceftaroline

fosamil to cynomolgus monkeys at up to 400 mg/kg had no significant effect on arterial blood pressure, heart rate or electrocardiogram (ECG) parameters. Neither ceftaroline (up to 300 μ M) nor ceftaroline fosamil (up to 100 μ M) affected action potential parameters of isolated canine Purkinje fibres. An IV dose of 200 mg/kg of ceftaroline fosamil in rats caused a transient increase in respiration rate and decrease in tidal volume but the minute volume was not affected. Doses of ceftaroline fosamil up to 600 mg/kg had no effect on water and electrolyte excretion by rats.

Pharmacokinetics

General

Systemic concentrations of ceftaroline were affected by the route of drug administration. Bioavailability of ceftaroline after oral (PO) compared to IV administration to dogs was less than 1%. Whilst studies in both rabbits and monkeys suggested a more prolonged exposure to high concentrations of ceftaroline after intramuscular (IM) compared to IV administration. Ceftaroline and ceftaroline M-1 had longer plasma half-lives than ceftaroline fosamil, in the species examined. Although values were quite variable between species, with ceftaroline having a half-life of 0.18, 0.43 and 1.16 h following IV administration of ceftaroline fosamil to rabbits, rats and cynomolgus monkeys, respectively (as compared to a half-life of 2.60 h in humans; Clinical Study P903-13). Repeat-dose studies in rats and cynomolgus monkeys of up to 13 weeks duration showed comparable pharmacokinetics between the sexes and at the start and conclusion of the dosing period, with no appreciable accumulation of ceftaroline fosamil or its metabolites.

Distribution

Ceftaroline showed relatively low plasma protein binding in all species examined. The mean fraction of ceftaroline bound to human plasma protein in the concentration range 1-50 μ g/mL was approximately 20%. A similar fraction of drug was bound by monkey plasma protein. Radiolabelled ceftaroline fosamil showed low level tissue uptake and rapid removal from the body following IV administration to rats. However, the drug was shown to penetrate lung tissue in rabbits and to thereby have potential for treatment of pneumonia. Very little radioactivity remained in all rat tissues by 72 h post dose and there was no persistence of radioactivity in eye or pigmented skin.

Metabolism

In vitro incubation of ceftaroline fosamil with plasma from humans or other species resulted in the production of ceftaroline (the most significant metabolite) and ceftaroline M-1 (derived by hydrolysis of the β -lactam moiety of ceftaroline). The conversion of ceftaroline fosamil to ceftaroline was blocked by phosphatase inhibitors, suggesting the involvement of plasma phosphatase(s) in the metabolism of ceftaroline fosamil. Consistent with such results, analysis of plasma from various species (including humans), following IV injection of ceftaroline fosamil, identified the presence of ceftaroline (the major metabolite) and ceftaroline M-1. In contrast to its metabolism by plasma, ceftaroline fosamil was stable when incubated with hepatic microsome suspension from humans or other species. This result suggested that CYP450 enzymes do not have a significant role in the metabolism of ceftaroline fosamil.

Excretion

Studies were conducted in rats and cynomolgus monkeys using IV administration of radiolabelled ceftaroline fosamil. Excretion of ceftaroline fosamil and/or its metabolites

was predominantly (approximately 90%) via urine in rats. For cynomolgus monkeys, excretion was via both urine and faeces. Human data was similar to that for rats and indicated that approximately 90% of radioactivity was excreted in urine.

Conclusion

The pharmacokinetic studies were primarily performed with rats and cynomolgus monkeys. As noted above, both species showed similarities and differences from humans in their drug responses. Nevertheless, in combination these two species should provide reasonable models for evaluating possible ceftaroline fosamil-induced toxicity in humans.

Pharmacokinetic drug interactions

Studies using human liver microsomes or microsomes from cell lines expressing a human CYP cDNA showed that neither ceftaroline fosamil nor ceftaroline (at concentrations up to 100 µmol/L) produced significant inhibition of chemical reactions catalysed by the major CYP isoforms. Based on a C_{max} for ceftaroline of approx. 35-50 µM at the therapeutic dose of 600 mg twice daily, inhibition of CYP activity by ceftaroline is unlikely to be a clinical issue. Exposure of primary cultures of human hepatocytes to clinically relevant concentrations of ceftaroline fosamil or ceftaroline for three days had no significant effect on levels of activity of the major CYPs; although 50 µM ceftaroline M-1 produced an approximate 5-fold increase in CYP1A2 activity. Based on these results, ceftaroline fosamil is not expected to significantly alter the metabolism by CYP enzymes of co-administered drugs.

Ceftaroline was not a substrate of the renal transporters OCT2, OAT1 and OAT3, and nor did it alter the transport of substrates of these proteins. Ceftaroline fosamil was, however, an OCT2 substrate and inhibited the transport of another substrate of this protein. Such inhibition was modest and unlikely to be of clinical significance because of the rapid conversion of ceftaroline fosamil to ceftaroline under *in vivo* conditions. It was concluded that renal elimination of ceftaroline is unlikely to be affected by co-administered drugs that inhibit these transporters and that conversely, ceftaroline is not expected to inhibit the clearance of drugs that are actively secreted by these transporters.

Neither ceftaroline fosamil nor ceftaroline was transported by P-gp or BCRP, although both compounds were weak inhibitors of BCRP at supra-therapeutic concentrations.

Toxicology

Acute toxicity

Single-dose toxicity studies were performed using rats and cynomolgus monkeys given IV doses of ceftaroline fosamil up to 2,000 mg/kg. Transient clinical signs included urine discolouration and mydriasis in both species, and prone position and tonic/clonic convulsions in rats given the high dose (HD). There were no mortalities for either species at the HD.

Repeat-dose toxicity

These studies were performed with rats and cynomolgus monkeys given a daily IV dose of ceftaroline fosamil at therapeutic to supra-therapeutic levels for 2, 4 or 13 weeks. The

duration of the pivotal studies, the species used, the group sizes and so on, were consistent with the relevant European Medicines Agency (EMA) guideline¹.

Relative exposure

Plasma exposure ratios were calculated using animal area under the plasma concentration time curve (AUC) between zero h and 24 h ($AUC_{0-24\text{ h}}$) values and the AUC value from Clinical Study P903-13, in which male volunteers received a single IV dose of 600 mg of ceftaroline fosamil. The latter value was multiplied by two to approximate the exposure from a clinical dose of 2 x 600 mg of ceftaroline fosamil per 24 h. As shown in the table below, relative exposures at the No observable adverse effect level (NOAEL) were around unity for the rat toxicity studies, and were similar, although rather variable (0.3-2.8), for the monkey studies.

Table 2. Relative exposure to ceftaroline in repeat-dose toxicity studies. Table continued across 2 pages.

Species	Study duration (number)	Dose (mg/kg/day)	$AUC_{0-24\text{ h}}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	Exposure ratio ^a
Rat (SD)	2 weeks (TAK-599/00081)	40 (day 1)	52.5, 54.7 ^b	0.4, 0.4 ^b
		40 (day 14)	53.1, 28.7	0.4, 0.2
		120 (day 1)	135.3, 151.0	1.1 ^c , 1.2
		120 (day 14)	137.0, 78.9	1.1 , 0.6
		400 (day 1)	391.5, 371.5	3.1, 2.9
		400 (day 14)	423.8, 251.8	3.3, 2.0
	4 weeks (TAK-599/00015)	100 (day 1)	85.3, 91.7	0.7 , 0.7
		100 (day 29)	130.4, 118.6	1.0 , 0.9
		300 (day 1)	190.1, 236.0	1.5, 1.8
		300 (day 29)	321.4, 292.6	2.5, 2.3
		1,000 (day 1)	660.4, 803.1	5.2, 6.3
	4 weeks (CXL-TX-02)	1,000 (day 29)	655.2, 825.3	5.1, 6.5
		50 (day 1)	61.0, 69.3	0.5, 0.5
		50 (day 28)	62.8, 65.8	0.5, 0.5
		100 (day 1)	131.0, 130.3	1.0, 1.0
		100 (day 28)	113.8, 131.9	0.9, 1.0
	13 weeks (P0903-T-010)	200 (day1)	223.3, 232.4	1.8 , 1.8
		200 (day 28)	193.4, 209.1	1.5 , 1.6
		30 (day 1)	26.3, 23.0	0.2, 0.2
		30 (day 91)	47.2, 41.9	0.4, 0.3
90 (day 1)		64.2, 68.8	0.5 , 0.5	
90 (day 91)		111.0, 105.0	0.9 , 0.8	
270 (day 1)	210.0, 202.0	1.6, 1.6		
	270 (day 91)	247.0, 287.0	1.9, 2.2	
	2 weeks (TAK-599/00082) ^d	40 (day 1)	139.9, 105.2	1.1, 0.8
		40 (day 14)	122.9, 97.1	1.0, 0.8
120 (day 1)		449.0, 379.8	3.5, 3.0	
120 (day 14)		371.3, 362.5	2.9, 2.8	

¹ Guideline on repeated dose toxicity. CPMP/SWP/1042/99 Rev 1
<<http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf>>

Species	Study duration (number)	Dose (mg/kg/day)	AUC _{0-24 h} (µg·h/mL)	Exposure ratio ^a
		400 (day 1)	1,529.1, 1,213.6	12.0, 9.5
		400 (day 14)	1,558.0, 1,547.1	12.2, 12.1
	4 weeks (TAK-599/00037)	16 (day 1)	47.5, 42.2	0.4, 0.3
		16 (day 28)	42.1, 41.0	0.3, 0.3
		80 (day 1)	222, 299	1.7, 2.3
		80 (day 28)	194, 216	1.5, 1.7
		400 (day 1)	1,083, 1,116	8.5, 8.7
		400 (day 28)	1,188, 1,104	9.3, 8.7
	4 weeks (CXL-TX-03)	20 (day 1)	49.9, 52.3	0.4, 0.4
		20 (day 28)	60.8, 63.3	0.5, 0.5
		50 (day 1)	143.9, 144.4	1.1, 1.1
		50 (day 28)	192.6, 178.1	1.5, 1.4
		100 (day 1)	305.3, 280.4	2.4, 2.2
	13 weeks (P0903-T-011)	100 (day 28)	314.8, 360.4	2.5, 2.8
		8 (day 1)	13.7 ^e	0.1
		8 (day 90-92)	10.8	0.1
		16 (day 1)	27.0	0.2
		16 (day 90-92)	26.0	0.2
		32 (day 1)	72.2	0.6
	32 (day 90-92)	42.6	0.3	
	64 (day 1)	157.0	1.2	
64 (day 90-92)	110.0	0.9		
Human (healthy ♂ volunteers)	single IV dose (P903-13)	[600 mg]	63.8 x 2	-

a = animal:human plasma AUC_{0-24 h} (human value = 600 mg x 2); b = ♂, ♀ values; c = bolded and underlined figures are exposure ratio at NOAEL; d = NOAEL for this study was less than LD; e = combined data for ♂ and ♀

Major toxicities

The major target organ for ceftaroline fosamil in both rats and monkeys was the kidney, with effects also observed on bladder, central nervous system, gastrointestinal tract and lymphoid organs.

Renal effects of ceftaroline fosamil dosing were seen in rat 4- and 13-week and in monkey 2 and 4 week IV repeat-dose toxicity studies. These effects included deposition of granular material and vacuolation of the epithelium of renal collecting tubules and inflammatory cell infiltration of kidney tubules. These changes showed a reduction in severity following a one month non-dosing period. Similar outcomes were seen in the urinary bladder, with accumulation of foreign material and hyperplasia of the transitional epithelium noted after 4 week repeat dosing of rats at 1,000 mg/kg. Renal changes in animals occurred at ceftaroline plasma AUC values comparable with human values after a therapeutic dose. However, the kidneys of animals showing these changes had been eliminating each day at least 3 times the amount of ceftaroline fosamil and its metabolites (on a mg of drug per kg of body weight basis), and for a longer period, as compared with proposed human therapeutic use. (As noted above, the plasma half-life of ceftaroline is significantly longer in humans as compared with rats or monkeys.) Hence, it is likely that renal effects

resulting from human therapeutic use would be less significant than those seen in animal experiments.

Clonic/tonic convulsions occurred in both rats and monkeys during the single and repeat dose studies. This finding was sometimes associated with mortality, although the mechanism of death was unclear. Induction of convulsions in both species occurred following administration of high doses of ceftaroline fosamil: a single dose of 1,000-2,000 mg/kg in rats or after multiple doses of 270 mg/kg or 400 mg/kg in rats and monkeys, respectively. The latter two doses were estimated to produce peak plasma concentrations (C_{max}) levels around 10-20-times those in humans given a therapeutic dose of 600 mg of ceftaroline fosamil (mean C_{max} in humans was 27.35 $\mu\text{g/mL}$ - Clinical Study P903-13). Hence, convulsions are expected to be a less significant risk at the test article concentrations associated with clinical use.

Repeat dosing of rats and monkeys with ceftaroline fosamil produced an increase in spleen weight and an enlargement of germinal centres in splenic lymph nodules. This change was mainly seen in the higher dose groups. It may reflect an inflammatory response and appeared to reverse during a post-dosing recovery period. It is unlikely that this response has clinical relevance due to the shorter period of human therapeutic dosing and the lower doses employed clinically. Some studies also noted liver enlargement after ceftaroline fosamil dosing, although this outcome was not correlated with histopathological changes.

A common finding, particularly in animals given high doses of the test article, was loose stools. This effect presumably reflects a change in the intestinal flora balance caused by the antibacterial action of the test article. An *in vitro* human gut model was used to examine the potential for *Clostridium difficile* (the most serious cause of antibiotic-associated diarrhoea in humans) infection following ceftaroline treatment. Germination and proliferation of *Clostridium difficile* spores, followed by cytotoxin production, were demonstrated following cessation of ceftaroline dosing and it was concluded that the test article has the potential to induce *Clostridium difficile* infection in the gut. The ceftaroline PI has an appropriate statement regarding this possibility in the *Precautions* section.

Haematologic parameters showed little or no effect of ceftaroline fosamil dosing in both rats and monkeys.

Genotoxicity

Ceftaroline and/or ceftaroline fosamil were tested for mutagenicity (both bacterial and mammalian cell assays), clastogenicity (towards mammalian cells growing in culture and in both mice and rats using the bone marrow micronucleus assay), and induction of deoxyribonucleic acid (DNA) repair (measurement of unscheduled DNA synthesis in hepatocytes from rats dosed with ceftaroline fosamil). The range of genotoxicity assays performed and the test article concentrations examined were appropriate. The test article was inactive in mutagenesis assays but was active in *in vitro* chromosomal aberration assays and was possibly active in the unscheduled DNA synthesis assay². It is, however, unlikely that ceftaroline fosamil poses a genotoxic risk to patients as its clastogenicity in *in vitro* assays occurred at supra-clinical concentrations and was markedly reduced/eliminated by the presence of rat liver S9 fraction.³

² Sponsor clarification: "In the UDS assay, although the number of cells in repair was greater than the negative control ($\leq 6.2\%$), the results of the study were considered negative by the reporting laboratory due to not meeting the positive criterion of 20% or greater."

³ S9=Supernatant fraction obtained from an organ (usually liver) homogenate. This fraction contains cytosol and microsomes. Chemical substances such as medicines sometimes require metabolic activation in order to become mutagenic and the metabolic enzymes of bacteria used in the Ames test differ substantially from those in mammals. Therefore to mimic the metabolism of test substance that would occur in mammals, the S9 fraction is often added to the Ames test.

Carcinogenicity

No carcinogenicity studies were presented by the sponsor. This is acceptable given the relatively short period of patient treatment with ceftaroline fosamil and the drug's limited activity in genotoxicity assays⁴.

Reproductive toxicity

Experiments were performed on rats and rabbits and examined possible effects of IV dosing with ceftaroline fosamil on fertility, embryofetal development, and pre/postnatal development. These studies used standard species, appropriate group sizes, and appropriate timing and duration of treatment.

Relative exposure

Table 3 shows the human: animal relative plasma exposure in the reproductive studies.

Table 3. Relative exposure in Reproductive studies

Species	Study	Dose (mg/kg/day)	AUC _{0-24 h} (µg·h/mL)	Exposure ratio ^a
Rat (SD)	Embryofetal development (CEF-TX-10)	100	131, 172 ^b	1.0, 1.3
		300	342, 471 ^b	2.7, 3.7
Rabbit (NZW)	Embryofetal development (CEF-TX-14)	25	22.8, 43.4 ^c	0.18, 0.34
		50	79.8, 83.5 ^c	0.63, 0.65
Human (healthy ♂ volunteers)	single iv dose (P903-13)	[600 mg]	63.8 x 2	–

^a = animal:human plasma AUC_{0-24 h} (human value = AUC at 600 mg x 2); ^b = GD6 and GD17 values; ^c = GD6 and GD18 values.

Rat studies used HD values that achieved exposures several times those expected for humans given 1,200 mg of ceftaroline fosamil per 24 h (see table above). Such doses had no adverse effect on rat fertility, embryofetal development, or pre-/postnatal development, although they could produce parental toxicity. Rabbit embryofetal studies were limited by maternal toxicity to doses that gave exposures lower than those expected in humans (see table). This toxicity manifested as deaths and abortions that were associated with body weight loss and were presumed to reflect a secondary effect of the test article's activity towards the intestinal flora. Fetuses from groups showing these effects had an increased incidence of angulated hyoid alae, a variation or delay in skeletal development. This developmental variation was considered a secondary effect of the test article's activity towards the intestinal flora and the sensitivity of the rabbit to such disturbance.

No studies were performed to examine possible placental transfer and excretion in milk of ceftaroline fosamil and its metabolites.

⁴ Guideline on the need for carcinogenicity studies of pharmaceuticals S1A.
<http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf>

Pregnancy classification

The sponsor has proposed Pregnancy Category B1⁵. This category is appropriate given the apparent lack of significant effects of the test article on embryofetal development in animal models. The US pregnancy category is B.

Local tolerance

Daily IM injection of a clinical preparation of ceftaroline fosamil for ten consecutive days was well tolerated by rabbits. Changes at the injection site were comparable for animals given the test article or vehicle control. The test article did not induce pathological changes. IV infusion of ceftaroline fosamil was also well tolerated by rabbits and did not produce local irritation at the injection site.

Antigenicity

Guinea pigs given multiple IV doses of ceftaroline fosamil (with or without Freund's complete adjuvant) did not show symptoms of active systemic anaphylaxis when, two weeks later, challenged with ceftaroline fosamil. However, intradermal (ID) injection of serum from animals that received ceftaroline fosamil plus Freund's complete adjuvant into untreated recipient animals, produced passive cutaneous anaphylaxis in some cases. It was concluded that ceftaroline fosamil is normally not antigenic but can be antigenic under conditions of enhanced immune function. Allergic reactions to cephalosporins are a known class-effect, particularly in individuals with sensitivity to other β -lactam antibiotics. The ceftaroline PI contains appropriate statements regarding this possibility in the Contraindications and Precautions sections.

Impurities

Fourteen chemicals were identified as real or potential impurities in ceftaroline fosamil drug substance or product. Some of these impurities were qualified through specific toxicity studies or through being a metabolite of ceftaroline fosamil.

Proposed limits for several impurities in the drug product exceed the ICH qualification threshold. Two impurities were not toxicologically qualified due to inadequate exposures in animal toxicity studies. Another two impurities and an arginine adduct were adequately tested in animal toxicity studies, with negative results. The lack of toxicological qualification of several impurities might be acceptable on clinical grounds, due to the recommended short duration of treatment (7-14 days) for potentially serious infections.

Paediatric use

Use of ceftaroline fosamil in patients <18 years of age is not being sought as part of this submission. A study of test article dosing of juvenile rats revealed no toxicologically or physiologically meaningful changes at IV doses up to 270 mg/kg/day.

Nonclinical summary and conclusions

- The nonclinical studies are comprehensive and of high quality and have been performed by reliable laboratories. The crucial toxicological studies were performed to GLP standard.
- Ceftaroline bound most PBPs from *Staphylococcus aureus* and *Streptococcus pneumoniae* strains, with an affinity comparable to or higher than comparator antibiotics. It showed bactericidal activity towards a range of Gram-negative and

⁵Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

-positive bacteria, under both *in vitro* and *in vivo* conditions. Ceftaroline showed similar or greater effectiveness than linezolid and vancomycin in treating bacterial species and strains that are frequently implicated in the proposed clinical indications for ceftaroline therapy.

- In secondary pharmacodynamics studies, the only targets that showed significant responses were human Cav1.2 voltage-gated cardiac ion channel and hERG-encoded ion channel. Both showed weak inhibition at ceftaroline fosamil concentrations that far exceeded the expected clinical plasma levels. Ceftaroline fosamil doses of 2,000 mg/kg could induce tonic convulsion in rats, and doses of 200 mg/kg or greater had a proconvulsant effect (significantly decreasing the time of onset of pentylenetetrazole-induced seizure in rats). Again, the practical significance of these findings is uncertain because of the relatively high doses employed. Germination and proliferation of *Clostridium difficile* spores, followed by cytotoxin production, were shown to occur following cessation of ceftaroline dosing in an *in vitro* gut model and it was concluded that the test article has the potential to induce antibiotic-associated diarrhoea.
- Data from rats and cynomolgus monkeys showed comparable pharmacokinetics between the sexes and at the start and conclusion of daily dosing periods of up to 13 weeks. These studies showed no appreciable accumulation of ceftaroline fosamil or its metabolites. Intramuscular infusion appeared to be the most effective method of drug administration. Ceftaroline fosamil showed low level tissue uptake and relatively rapid removal from the body following IV administration to rats.
- Repeat-dose toxicity studies, using rats and cynomolgus monkeys, identified the kidney as the major target organ for ceftaroline fosamil. Effects were also observed on bladder, central nervous system, gastrointestinal tract and lymphoid organs. Due to the greater exposure time and doses used in animal studies compared with clinical use, it was not expected that these effects would be major issues for patients. In addition, the effects seen in kidney were at least partly reversed during a one month, drug-free, recovery period.
- Ceftaroline/ceftaroline fosamil gave negative results in mutagenicity assays but was active in *in vitro* chromosomal aberration assays (albeit at supra-therapeutic concentrations). No carcinogenicity studies were presented by the sponsor. This is acceptable given the relatively short period of patient treatment with ceftaroline fosamil and the drug's limited activity in genotoxicity assays.
- Reproductive toxicity studies using rats showed no adverse effects of ceftaroline on fertility, embryofetal development, or pre/postnatal development. Rabbit studies showed maternal toxicity and an increased incidence of angulated hyoid alae in fetuses, however, these effects were attributed to the sensitivity of the rabbit to disturbance of its intestinal flora.
- Guinea pig studies suggested that ceftaroline fosamil is not normally antigenic but can be antigenic under conditions of enhanced immune function.
- Two impurities with proposed limits above the ICH qualification threshold were not adequately qualified in nonclinical toxicity studies due to low exposure ratios but may be acceptable on clinical grounds due to the short period of patient treatment.

Conclusions and recommendation

- Aside from the lack of adequate toxicological qualification of two impurities, the dossier of studies had no major deficiencies.

- The combination of primary pharmacology studies and demonstrations of ceftaroline's bactericidal efficacy in both *in vitro* and *in vivo* assays, supports its use for the proposed clinical indications.
- With the exception of antibiotic-associated diarrhoea, no clinically relevant hazards were identified in the secondary pharmacodynamics and safety pharmacology studies as occurring at ceftaroline concentrations approximating expected clinical plasma levels.
- Repeat-dose toxicity studies identified the kidney as the major target organ, however, it was unclear whether this finding was of clinical significance.
- Ceftaroline/ceftaroline fosamil is not considered to pose a genotoxic or carcinogenic hazard.
- The lack of significant effects of the test article on embryofetal development support its proposed placement in Pregnancy Category B1.
- There are no nonclinical objections to registration.
- Recommendations to the draft PI were made but these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

The sponsor provides the following rationale in support of the application:

"There remains a persistent and growing unmet medical need for new antibiotics that provide efficacy in the treatment of patients with cSSTI and CAP. cSSTIs that require hospitalization or medical attention are increasing in incidence, and despite advances in medical care and antimicrobial therapy, CAP remains an important cause of mortality and hospitalization throughout the world. New antimicrobials with an enhanced spectrum of activity are needed for such serious infections, especially given the rising incidence of highly resistant and highly virulent pathogens such as MRSA, vancomycin intermediate and resistant *S. aureus* (VISA and VRSA), and MDRSP. Zinforo addresses this distinct area of unmet medical need."

Scope of the clinical dossier

The submission contained the following clinical information:

Clinical

- There were five pharmacokinetic studies conducted in healthy subjects: Study P903-13, Study P903-01, Study P903-17, Study P903-20, and Study CXL-PK-01. There were five pharmacokinetic studies investigating the effects of intrinsic factors: Study P903-02, Study P903-04, Study P903-18, Study P903-15, and Study 903-11. There were eight population pharmacokinetic studies: Study P903-HP-001, Study P903-HP-002, Study P903-HP-003, Study 00174-1, Study 00174-2, Study 00174-3, Study 00174-4, and Study 00174-5.
- There was one thorough QT study: Study P903-05.
- There was one study of the effect of ceftaroline on enteric bacteria: Study P903-14
- There were five simulation studies, using the models derived from the population pharmacokinetic studies: Study 00174-6, Study 00174-7, Study 00174-8, Study 00174-

9 and a study entitled “Technical Report: Supplementary target attainment analysis for patients with infection of cSSTI and CAP”.

- There were two Phase II studies conducted, both for the indication of cSSTI: Study P903-03 and Study P903-19
- There were two Phase III studies conducted for the indication of cSSTI: Study P903-06 and Study P903-07
- There were two Phase III studies conducted for the indication of CAP: Study P903-08 and Study P903-09
- There were no additional clinical studies evaluable only for safety.

Paediatric data

The submission included paediatric pharmacokinetic data for age 12 years and older. However, the sponsor has not applied for the indication to include paediatric patients.

Good clinical practice

All the clinical studies presented in the dossier were stated to have been conducted in accordance with Good Clinical Practice.

Pharmacokinetics

Summary of pharmacokinetics

Mean (SD) total recovery of intravenously administered ceftaroline fosamil is 93.4% (3.1%), with recovery from urine of 87.5% (3.9%) and faeces of 5.95 (2.93%). The mean percent of dose excreted in urine as ceftaroline is approximately 65%. Systemic exposure to ceftaroline prodrug and ceftaroline M-1, as determined by AUC, is about 2.5% and 20%, respectively, of the systemic exposure of ceftaroline.

The pharmacokinetics of ceftaroline fosamil administered intramuscularly (IM injection concentration: 228 mg/mL) were dose proportional with a time to peak plasma concentration (T_{max}) of 1.5 to 2 hours.

For intravenous ceftaroline fosamil there was dose proportionality for C_{max} and AUC across the dose range 600 mg to 2000 mg. The half life ($t_{1/2}$) was stable across this dose range at around 2.5 hours, as was clearance at around 7 L/hour.

Ceftaroline AUC and C_{max} increased with impairment of renal function, with an increase of around 10% in C_{max} and 50% in AUC in moderate renal impairment. In severe renal failure ceftaroline C_{max} increased by approximately 21%, AUC increased by 115%, $t_{1/2}$ increased by 67% and clearance decreased by 53%. Clearance of ceftaroline was decreased by 63% in ESRD. Clearance of ceftaroline fosamil was decreased by 50% with pre-dialysis administration and by 90% with post-dialysis administration. There was markedly increased exposure to ceftaroline M-1 with a doubling of C_{max} and tripling of AUC with moderate renal impairment. In severe renal failure, Ceftaroline M-1 C_{max} increased by 120%, AUC increased by 300%, $t_{1/2}$ increased by 60% and clearance decreased by 74%.

In healthy elderly subjects (age ≥ 65 years) ceftaroline C_{max} was similar to that for healthy young subjects but AUC was increased by 33% in the elderly group and ceftaroline clearance was decreased by 32%. In adolescent subjects clearance was increased to 14 L/h.

In the population pharmacokinetic studies, the main covariate influencing the renal clearance of ceftaroline was creatinine clearance (CrCl) and the main influence on volume of distribution was body weight. Simulations predicted that in mild renal impairment

(CrCl >50–80 mL/min) no dosage adjustment was necessary (600 mg at twelve hourly intervals (q12h) administered over 1 hour); in moderate renal impairment (CrCl >30–50 mL/min) the dose should be adjusted to 400 mg q12h, administered over 1 hour; and in severe renal impairment (CrCl ≤ 30 mL/min) no formal dosage adjustment was proposed, but dose adjustment to 300 mg q12h over 1 hour may be adequate. For ceftaroline, there was an increase in the central volume of distribution of 8.97 L (1.81 fold) in Phase II/III and of peripheral volume of distribution of 3.65 L in the Phase II/III subjects. There was an increase in clearance of 5.24 L/h (1.36 fold) in the phase II/III subjects.⁶

Evaluator’s overall conclusions on pharmacokinetics

The pharmacokinetics of ceftaroline fosamil were adequately characterised in adult subjects.

Pharmacodynamics

Summary of pharmacodynamics

The Thorough QT study did not indicate an effect of ceftaroline on QTc.⁷

Ceftaroline did have an altering effect on the populations of enteric bacteria. It is not clear what the clinical significance of the alterations is but there is a potential for *Clostridium difficile* colitis to occur as an adverse event (AE).

The simulation studies provided support for the dosing regimens used in the Phase III studies.

Evaluator’s overall conclusions on pharmacodynamics

The pharmacodynamics of ceftaroline were adequately characterised in the clinical studies.

Efficacy

Dosage selection for the pivotal studies

The dosage selection for the pivotal studies was developed from the pharmacokinetic and pharmacodynamic studies.

Evaluators conclusions on efficacy

Clinical efficacy for cSSTI

In Study P903-06 non-inferiority was demonstrated in comparison with vancomycin:

⁶ Sponsor clarification: “For ceftaroline, there was an increase in the central volume of distribution of 8.97 L (1.81 fold) in Phase II/III subjects compared to Phase I subjects and an increase of peripheral volume of distribution of 3.65 L in male subjects compared to female subjects.. There was an increase in clearance of 5.24 L/h (1.36 fold) in the Phase II/III subjects compared to Phase I subjects.”

⁷Since 2005, the FDA and European regulators have required that nearly all new molecular entities are evaluated in a Thorough QT (TQT) study to determine a drug’s effect on the QT interval. See <<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf>>. 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. In general, the QT interval represents electrical depolarisation and repolarisation of the left and right ventricles. A lengthened QT interval is a biomarker for 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 QT interval) and needs to be corrected by heart rate (QTc) to evaluate the risk of ventricular arrhythmia.

Clinical cure rates appeared to be worse for ceftaroline in comparison with vancomycin in subjects >75 years age. There also appeared to be a poorer response for Gram negative organisms (see Sponsor clarification⁸ and Table 3 in PI).

In Study P903-07 non-inferiority was also demonstrated for ceftaroline in comparison with vancomycin. However, in this study clinical cure rates appeared to be better for ceftaroline in comparison with vancomycin in subjects >75 years age. There also appeared to be a poorer response for Gram negative organisms (see Sponsor clarification⁹ and Table 3 in PI).

Although Study P903-03 had insufficient sample size for hypothesis testing, the results supported the efficacy of ceftaroline in comparison with vancomycin in subjects with cSSTI.

Study P903-19 investigated a different route of administration (intramuscular) and used linezolid as a comparator. Response rates appeared to be poorer for intramuscular ceftaroline than linezolid or intravenous ceftaroline, when compared with the results from the other efficacy studies. However, the sponsor has not requested approval of the intramuscular administration route in the present application.

The pooled analysis of the efficacy studies supported the efficacy of ceftaroline for the treatment of cSSTI due to MRSA. Four subjects in the ceftaroline group, and none in the comparator had a pathogen showing decreased susceptibility through to the test of cure (TOC) visit¹⁰.

In the pivotal efficacy studies, the non-inferiority criteria were sufficiently robust and adequately justified. The outcome measures were well designed. The sampling frame for subject selection was appropriate and resulted in a treatment population sufficiently representative of the treatment population in Australia.

The comparators used in the efficacy studies would not normally be first line treatment for cSSTI in Australia. Such infections would normally be treated with flucloxacillin as a first line agent. Vancomycin would be used as a second line agent and for patients with penicillin allergy. Linezolid would normally be reserved as a third line agent. Aztreonam would not normally be used to treat cSSTI in Australia.

Clinical efficacy for CAP

In Study P903-08, non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone, when clarithromycin was also used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline population for *Staphylococcus aureus* and *Streptococcus pneumoniae*.

In Study P903-09, non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone, when clarithromycin was not used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline population for *Staphylococcus aureus* and *Streptococcus pneumoniae*.

Although superiority testing was not intended in the study protocols, the pooled analysis indicated superiority for ceftaroline in comparison with ceftriaxone. In the modified

⁸ Sponsor clarification: "Ceftaroline showed a lower clinical cure rate than the comparator for overall Gram-negative organisms in the pooled cSSTI studies (refer Table 3 of the PI), which included patients infected with *P. aeruginosa* and *Proteus* spp. Clinical cure rates for ceftaroline were numerically higher than the comparator for some Gram-negative organisms (Table 3 of the PI)."

⁹ Sponsor clarification: "Ceftaroline showed a lower clinical cure rate than the comparator for overall Gram-negative organisms in the pooled cSSTI studies (refer Table 3 of the PI), which included patients infected with *P. aeruginosa* and *Proteus* spp. Clinical cure rates for ceftaroline were numerically higher than the comparator for some Gram-negative organisms (Table 3 of the PI)."

¹⁰ Sponsor clarification: "The pathogens in these 4 cases were *S. agalactiae*, *P. aeruginosa*, *E. cloacae* and *P. mirabilis*. Only 1 pathogen (*E. cloacae*) showed decreased susceptibility on repeated testing."

intention to treat efficacy (MITTE) population ceftaroline was superior to ceftriaxone for clinical response at TOC: 479 (82.6%) subjects in the ceftaroline group compared with 439 (76.6%) in the ceftriaxone, weighted difference (95% CI) 6.0% (1.4% to 10.7%).

In the pivotal efficacy studies, the non-inferiority criteria were sufficiently robust and adequately justified. The outcome measures were well designed. The sampling frame for subject selection was appropriate and resulted in a treatment population sufficiently representative of the treatment population in Australia.

The comparator used in the efficacy studies (ceftriaxone) would not normally be first line treatment for CAP in Australia. Such infections would normally be treated with penicillin as a first line agent, unless the patient's condition was severe. Ceftriaxone would usually be used for hospital acquired pneumonia rather than CAP in the Australian setting.

Safety

Studies providing evaluable safety data

Safety data were provided from all of the clinical studies that were performed in support of pharmacokinetics, pharmacodynamics and efficacy.

Pivotal studies that assessed safety as a primary outcome

There were no additional studies assessing safety as the primary outcome.

Patient exposure

There were a total of 1470 subjects exposed to ceftaroline fosamil in Phase II and Phase III trials during the development program. This included 613 with CAP and 857 with cSSTI. There were no subjects aged less than 18 years included in the Phase II and Phase III trials. There were 402 subjects age 65 years or more, including 188 subjects aged 75 years or more. There were 117 subjects with creatinine clearance >30 and ≤50 mL/min and 15 subjects with creatinine clearance of ≤30 mL/min. There were 169 subjects with hepatic impairment and 287 with cardiac impairment.

Patient exposure in cSSTI

In Study P903-03 there were 67 subjects treated with ceftaroline fosamil. The duration of treatment was, median (range), 6.7 (0.4 to 19.5) days in the ceftaroline group and 7.4 (2.0 to 20.5) in the comparator.

In Study P903-06 351 subjects with cSSTI were exposed to ceftaroline with a median (range) duration of exposure of 7.0 (0.5 to 18.0) days. One subject was exposed for 15 days or more.

In Study P903-07, a total of 341 subjects received ceftaroline for the indication of cSSTI. The median (range) duration of exposure was 6.5 (0.5 to 21.0) days.

In Study P903-19, a total of 98 subjects with cSSTI were exposed to ceftaroline 600 mg q12h for a median (range) of 6.50 (0.5 to 13.0) days.

Patient exposure in CAP

In Study P903-08, a total of 298 subjects with CABP were exposed to ceftaroline for a median (range) of 6.5 (0.5 to 7.5) days. No subjects were exposed to ceftaroline for more than 8 days.

In Study P903-09 a total of 315 subjects with CABP were exposed to ceftaroline for a median (range) of 6.0 (1.0 to 7.0) days. No subjects were exposed to ceftaroline for more than 8 days.

Postmarketing experience

The Important identified risks are:

- Clostridium difficile colitis
- Hypersensitivity/Anaphylaxis

The Important potential risks are:

- Bacterial resistance development
- Convulsion/Seizures; based on class effects mainly seen with concurrent renal failure and some nonclinical findings
- Drug-induced liver injury; based on observance of transient increases in liver enzyme levels
- Haemolytic anaemia; based on class effects and observance of positive direct antiglobulin tests (also referred to as a positive Coombs' test)
- Renal impairment (including potential drug interactions with nephrotoxic agents); based on class effects and observance of increased serum creatinine levels

The safety data did not indicate any additional identified or potential risks.

Evaluator's overall conclusions on clinical safety

Treatment Emergent AEs (TEAEs) were reported in around 60% of subjects and occurred at a similar rate to comparator treatment. Headache occurred in up to 16% of subjects, nausea 12%, and diarrhoea 5%.

In the Phase I studies, the rates of TEAEs increased with dose and the level of tolerability appeared to be 600 mg q12h.

Urine discolouration and odour occurred at the 600 mg q12h dosing level. Some subjects reported body odour. Injection site AEs (pain/discomfort/thrombophlebitis) occurred in approximately 40% of subjects.

Ceftaroline did not appear to be associated with QT prolongation in either the Thorough QT study or in the other clinical studies.

Ceftaroline did not appear to be associated with seizures or hepatobiliary dysfunction.

Serious AEs (SAEs) were uncommon and were not usually attributable to the study treatment. In Study P903-07, anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects, and were attributed to ceftaroline.

Death was uncommon and none were attributed to study treatment.

Ceftaroline appeared to be well tolerated with up to 5% of subjects discontinuing because of AEs but these were not usually attributed to the study treatment.

Up to 21% of subjects developed a positive direct Coomb's test during the course of treatment. However, this did not translate to an increased incidence of haemolytic anaemia.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

For the two indications sought in the present application ceftaroline had comparable efficacy to an acceptable standard of care for Australia. In subjects with cSSTI non-inferiority was demonstrated in comparison with vancomycin and in subjects with CAP non-inferiority was demonstrated in comparison with ceftriaxone. Efficacy was demonstrated for the intravenous route of administration at the dose level proposed for marketing.

Efficacy was demonstrated for conditions where there is a clinical need for new treatments. Ceftaroline had good efficacy against MRSA and also penicillin resistant strains of *Streptococcus pneumoniae*.

Although the comparators used in the efficacy studies would not normally be first line treatment for cSSTI or CAP in Australia the comparators do provide an acceptable standard of care for these conditions. Vancomycin would be used as a second line agent for cSSTI and first-line for patients with penicillin allergy, and linezolid would normally be reserved as a third line agent. Aztreonam is not usually used for the indication of cSSTI in Australia but is acceptable treatment for cSSTI resulting from Gram negative organisms. Ceftriaxone would not normally be first line treatment for CAP in Australia but would be an acceptable treatment for this indication and is commonly used for hospital acquired pneumonia in the Australian setting.

First round assessment of risks

Ceftaroline demonstrated an acceptable safety profile for an antibiotic in the Australian setting. TEAEs were reported in around 60% of subjects and occurred at a similar rate to comparator treatment. Headache occurred in up to 16% of subjects, nausea 12%, and diarrhoea 5%. The rates of TEAEs increased with dose and the level of tolerability appeared to be 600 mg q12h.

Urine discolouration and odour occurred at the 600 mg q12h dosing level. Some subjects reported body odour. Injection site AEs (pain/discomfort/thrombophlebitis) occurred in up to 40% of subjects.

Ceftaroline did not appear to be associated with QT prolongation in either the thorough QT study or in the other clinical studies. Ceftaroline did not appear to be associated with seizures or hepatobiliary dysfunction.

SAEs were uncommon and were not usually attributable to the study treatment. Anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects, and were attributed to ceftaroline.

Death was uncommon and none were attributed to study treatment.

Ceftaroline appeared to be well tolerated with up to 5% of subjects discontinuing because of AEs but these were not usually attributed to the study treatment.

Up to 21% of subjects developed a positive direct Coomb's test during the course of treatment. However, this did not translate to an increased incidence of haemolytic anaemia.

First round assessment of benefit-risk balance

The benefit-risk balance of ceftaroline, given the proposed usage, was considered favourable.

First round recommendation regarding authorisation

It was recommended that the following indication for ceftaroline fosamil (Zinforo) should be approved:

Zinforo is indicated for the treatment of the following infections in adults from the age of 18 years:

- *Complicated skin and soft tissue infections*
- *Community-acquired pneumonia*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns in the initial RMP which are shown at Table 4.

OPR reviewer comment

It is recommended that the 'Important other information-Potential for off-label use' be re-classified as an Important potential risk and the area of Important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' added to align with the RMP submitted to the European Medicines agency (EMA)¹¹.

Table 4. Summary of the Ongoing Safety Concerns as specified by the sponsor

Important identified risks	<i>Clostridium difficile</i> associated diarrhoea
	Hypersensitivity / Anaphylaxis
Important potential risks	Bacterial resistance development
	Convulsions / Seizures
	Drug-induced liver injury
	Haemolytic anaemia
	Renal impairment (including potential drug interactions with nephrotoxic agents)
Important missing information	Asian population exposure
	Immunocompromised population
	Lactation

¹¹ European Medicines Agency, EPAR Public Assessment Report for ceftaroline fosamil (Zinforo) [Ref; EMA/472628/2012] <<http://www.ema.europa.eu/ema/>>

	Longer than recommended duration of therapy
	Paediatric population exposure
	Pre-existing seizure disorder
	Pre-existing severe renal impairment
	Pre-existing significant hepatic disease
	Pregnancy exposure
Important other information	Potential for off-label use

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed to monitor all safety concerns. Additional pharmacovigilance activities (as provided in the initial RMP) are listed in Table 5 below.

Table 5. Additional pharmacovigilance activities. Table continued across 2 pages.

Additional activity	Assigned safety concerns	Actions/Outcome measures proposed	Planned submission of final data (if study)
Study D3720C00001	Important potential risks <ul style="list-style-type: none"> Haemolytic anaemia 	Haptoglobin and reticulocyte tests.	In development
	Important missing information <ul style="list-style-type: none"> Immunocompromised population Pre-existing seizure disorder Pre-existing severe renal impairment Pre-existing significant hepatic disease 	Evaluation of safety data. Eligibility for enrolment includes subjects with the following pre-existing conditions: <ul style="list-style-type: none"> Immunocompromised unless severely compromised Seizure disorders * CrCl \geq 15 mL/min** Hepatic impairment unless classified as Child Pugh Stage C 	
Study D3720C00002	Important potential risks <ul style="list-style-type: none"> Convulsions /Seizures Drug-induced liver injury Renal impairment (including potential drug interactions with nephrotoxic agents) Haemolytic anaemia 	Targeted follow-up questionnaires for adverse events of acute renal failure, convulsions / seizures, drug induced liver failure and haemolytic anaemia. Haptoglobin and reticulocyte tests (for Haemolytic anaemia).	Fourth quarter 2012

Additional activity	Assigned safety concerns	Actions/Outcome measures proposed	Planned submission of final data (if study)
	Important missing information <ul style="list-style-type: none"> Asian population exposure 	Evaluation of safety data	
Study D3720C00005	Important missing information <ul style="list-style-type: none"> Asian population exposure 	Evaluation of pharmacokinetic data	First Quarter 2012
Bacterial resistance surveillance programme	Important potential risks Bacterial resistance development Important other information <ul style="list-style-type: none"> Potential for off-label use 	Monitor changes in ceftaroline minimum inhibitory concentrations distributions among target pathogens (i.e. those pathogens identified in PI with clinical efficacy). Isolates will be collected from hospitals and medical centres across Europe, Latin America, Middle East-Africa and the Asia-Pacific Region. May also include isolates from other infection types and therefore explore off-label use.	In development
Targeted follow-up questionnaires for healthcare professionals	Important potential risks <ul style="list-style-type: none"> Convulsions /Seizures Drug-induced liver injury Renal impairment (including potential drug interactions with nephrotoxic agents) Haemolytic anaemia Bacterial resistance development Important other information <ul style="list-style-type: none"> Potential for off-label use 	Targeted questionnaires for adverse events of acute renal failure, convulsions /seizures, drug induced liver failure and haemolytic anaemia. In addition, a targeted questionnaire for when lack of effect is reported.	N/A
Paediatric investigational plan (PIP)	Important missing information <ul style="list-style-type: none"> Paediatric population exposure 	Evaluation of safety data produced by PIP	March 2017 (Study completion)

*AstraZeneca plans to add patients with pre-existing seizure disorders to all subsequent studies moving forward.

**A study to determine the appropriate ceftaroline fosamil dosing regimen in patients with end-stage renal disease.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

Bacterial resistance surveillance programme

A brief study synopsis of the Bacterial Resistance Surveillance Programme was provided with the RMP. However, the evaluator considers there is insufficient information provided to substantially evaluate this programme. It is recommended to the Delegate that the sponsor provide prior to marketing to the OPR a full study protocol/detailed protocol synopsis for this programme including study milestones for reporting to the TGA. It is also recommended to the Delegate that this programme include Australian sites to ensure it is adequately and appropriately representative of Australian isolates. Representation should include isolates from a great number of relevant Australian institutions (rather than many isolates from few sites). These recommendations are consistent with the advice provided by Advisory Committee on the Safety of Medicines (ACSOM), which should be also considered in the response provided by the sponsor.

Important missing information – 'Pre-existing severe renal impairment' and 'Immunocompromised population'

Study for dosing recommendations in ESRD (Study D3270C00012)

In the RMP the sponsor states that a study to determine the appropriate ceftaroline fosamil dosing regimen in patients with end-stage renal disease (ESRD) will be conducted, but that the protocol is still in development. In the EMA Assessment report for Zinforo¹¹, page 119 Table 31 [not in this AusPAR], the following is provided "The MAH shall provide a dosing recommendation for patients with creatinine clearance <30mL/min following study (D3270C00012) in ESRD after evaluating the PK and safety data derived from the phase 1 PK study D3270C00012 to determine the appropriate ceftaroline fosamil dosing regimen in patients with end stage renal disease." It was recommended that the sponsor provide to the OPR a full protocol/detailed protocol synopsis prior to marketing for this study, including study design, outcome measurements (primary and secondary), sample size, duration of treatment exposure, follow-up timepoints and inclusion/exclusion criteria. Study milestones for reporting to the TGA should also be provided. Furthermore, it was also recommended that a justification on how this study will further inform the area of Important missing information 'Pre-existing severe renal impairment' should also be provided.

Study D3720C00001

Patients with chronic renal impairment (creatinine clearance (CrCl) >15 ml/min to <50 ml/min) are eligible to participate in this study. However, inclusion of these patients is optional (see relevant inclusion criteria below). In addition, Study D3720C00001 is also assigned to the area of Important missing information 'Immunocompromised population', however, the inclusion of patients using immunosuppressive agents is also optional (see relevant inclusion criteria below). Given the inclusion criteria are optional it is recommended that the sponsor provide justification on how an adequate number of patients with these two conditions will be recruited into this study to further inform these two areas of Important missing information. Study milestones for D3720C00001 should be also provided to the TGA.

Inclusion criteria:

4. Subjects must have at least one of the following (for the first 4 bullets, criterion must be

met within 24 hours prior to randomization):

(note: vital signs must be recorded after a minimum of 10 mins rest with the patient in either seated or supine)

- Temperature $>38.0^{\circ}\text{C}$ (100.4°F) or $<36.0^{\circ}\text{C}$ (96.8°F), or
- White blood cells >12000 cells/ mm^3 or <4000 cells/ mm^3 or Greater than 10% band forms (immature white blood cells), or
- Heart rate >90 beats per minute and respiratory rate >20 breaths per minute after 10 mins of rest, or
- One or more of the following comorbidities
 - Diabetes mellitus requiring drug therapy.
 - Stage 2 or 3 HIV infection (per CDC classification 2008¹²) (except CD4 count <150 cell/microlitre within 6 months prior to randomization or suspected opportunistic infection are excluded).
 - Chronic renal impairment (CrCl >15 ml/min to <50 ml/min).
 - Cirrhosis with Child-Pugh Stage A or B. Patients with Child Pugh C are excluded.
 - cSSTI below the knee associated with peripheral vascular disease diagnosed on the basis of claudication at distance of 20 meters; or resting APBI 0.3-0.8; or prior femoral artery bypass grafting or prior aortic aneurysm repair.
 - Albumin <2.5 mg/dl or prealbumin <11 mg /dl in the absence of liver disease.
 - Use of immunosuppressive agents, including a glucocorticoid (but doses no greater than 40 mg/day of prednisone or equivalent for a maximum period of 1 week).
 - Malignancy other than non-melanoma skin cancers with life expectancy > 3 months.

Study D3720C00005

The sponsor states in the RMP that the planned date for submission of final data for Study D3720C00005 was first quarter of 2012. It is recommended that the sponsor provide an update on the timeline for the submission of this data to the TGA.

Study D3720C00010

In the RMP submitted to the EMA¹¹, Study D3720C00010 is assigned to the area of Important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset'. Study D3720C00010 does not appear in the GPRMP evaluated for the current submission. It was recommended to the Delegate that the sponsor provide prior to marketing to the OPR a study protocol, including outcome measurements (primary and secondary), follow-up timepoints, sample size, study duration and inclusion/exclusion criteria and study milestones for reporting to the TGA. In addition, a rationale on how this study will further inform the area of Important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' should also be provided. The GPRMP should be updated to reflect the addition of this study to the pharmacovigilance plan and provided to the OPR.

Targeted follow-up questionnaires for healthcare professionals and included in study

The targeted follow-up questionnaires were considered acceptable

¹² <<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a1.htm>>

Paediatric investigational plan

Zinforo is not recommended for use in patients under 18 years of age. The sponsor proposes to evaluate safety data produced by the paediatric investigation plan studies.

Risk minimisation activities

It is stated in the RMP, page 71 [not in this AusPAR]: *No risk minimisation activities beyond those considered routine are recommended for ceftaroline fosamil.*

OPR reviewer comment

Routine risk minimisation activities are considered acceptable.

Efficacy and safety in methicillin-resistant *Staphylococcus aureus* (MRSA) CAP has not been established, as patients with CAP due to MRSA were excluded from studies. The evaluator considers that this information is not adequately presented in the proposed Australian PI. It is important to clearly inform prescribers that the available clinical data does not support the use of Zinforo in CAP due to MRSA. Therefore, it is recommended that the Delegate consider adding the following precaution from the European Summary of product Characteristics (SmPC) (*Limitations of the clinical data*) to the precautions section of the proposed Australian PI (SmPC page 4 [not in this AusPAR]). This added precaution should be assigned in the RMP to the areas of Important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' and 'Immunocompromised population'.

"Limitations of the clinical data

There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT Risk Class V, and/or CAP requiring ventilation at presentation, CAP due to methicillin resistant S. aureus or patients requiring intensive care. Caution is advised when treating such patients.

There is no experience with ceftaroline in the treatment of cSSTI in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, necrotizing fasciitis, perirectal abscess and patients with third degree and extensive burns. There is limited experience in treating patients with diabetic foot infections. Caution is advised when treating such patients."

In addition, the evaluator considers that the presentation of susceptible pathogens in the proposed Australian PI may be misleading to prescribers to suggest that it could be used in all cases of MRSA. Therefore, to further guide and inform prescribers of the susceptible pathogens Zinforo has been demonstrated against, by indication, it is recommended the Delegate consider aligning the 'In vivo/in vitro susceptibility' section of the proposed Australian PI with the SmPC (*Clinical efficacy against specific pathogens* section).

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application.

It is recommended that the Delegate implement RMP Version 2, dated 18 November 2011, and any future updates as a condition of registration.

It is recommended to the Delegate:

Proposed indication

Given bacterial resistance is an important potential risk of Zinforo the evaluator considers that it is appropriate and practical for the Australian PI to recommend confirmation or strong suspicion of bacterial susceptibility prior to the initiation of treatment with Zinforo. It is recommended the Delegate consider amending the proposed indication to reflect this (please see suggestion below). In addition, it is also recommended that the words “empirical and directed” are removed from the indication, which may be less prone to misunderstanding by prescribers. Advice sought from ACSOM is consistent with these recommendations.

Zinforo is indicated for the treatment of patients with the following infections proven or strongly suspected to be caused by designated susceptible bacteria:

- *Complicated skin and soft tissue infections*
- *Community-acquired pneumonia*

Safety specification

That the sponsor align the Safety Specification of the submitted GPRMP with the RMP submitted to the EMA¹¹ by:

1. Reclassifying the ‘Important other information-Potential for off-label use’ as an Important potential risk.
2. Adding the area of Important missing information added ‘Potential for suboptimal dosing in patients with more severe systemic upset’.

The sponsor subsequently accepted the above recommendations as a regulatory imposition and updated the RMP Australian Specific Annex (ASA; Edition 2) accordingly. The OPR considered this acceptable in their Round 2 evaluation report.

Pharmacovigilance plan

Bacterial resistance surveillance programme

- That the sponsor provide to the OPR a full study protocol and study milestones for reporting to the TGA. This programme should include Australian sites to ensure it is adequately and appropriately representative of Australian isolates. Representation should include isolates from a great number of relevant Australian institutions (rather than many isolates from few sites; see Appendix 1: ACSOM advice).

The sponsor subsequently provided the final protocol and reporting periods to OPR. Australian sites will be included in the programme, as agreed with OPR.

Important missing information – ‘Pre-existing severe renal impairment’ and ‘Immunocompromised population’

Study for dosing recommendations in ESRD (Study D3270C00012)

- That the sponsor provide to the OPR a full protocol/detailed protocol synopsis for study D3270C00012 and milestones for reporting to the TGA. Furthermore, a justification on how this study will further inform the area of Important missing information ‘Pre-existing severe renal impairment’ should also be provided.

The sponsor subsequently provided the final protocol and reporting period to the OPR. A justification on how this study will further inform the area of Important missing information ‘pre-existing severe renal impairment’ was provided to, and accepted by the OPR.

Study D3720C00001

- Given the inclusion of patients with chronic renal impairment and immunosuppression is optional in Study D3720C00001, that the sponsor provide prior to marketing a justification on how an adequate number of patients with these two conditions will be recruited into this study to further inform these two areas of important missing information (see Table 6 below).

Table 6. Study D3720C00001

Important missing information	Relevant inclusion criteria from Study D3720C00001
Pre-existing severe renal impairment	Chronic renal impairment (CrCl >15 ml/min to <50 ml/min)
Immunocompromised population	Use of immunosuppressive agents, including a glucocorticoid (but doses no greater than 40 mg/day of prednisone or equivalent for a maximum period of 1 week)

- That the sponsor provides study milestones for D3720C00001. Milestones for this study were stated in the original RMP to be "*In development*".
- The sponsor subsequently provided a final protocol and reporting period to the OPR. A justification on how adequate number of patients with the two conditions will be recruited into this study to further inform the two areas detailed in Table 6 was provided to, and accepted by the OPR.

Study D3720C00005

- Provide an update on the timeline for the submission of this data to the TGA.
- The sponsor subsequently provided a revised reporting period to the OPR.

Study D3720C00010

- Provide to the OPR prior to marketing a study protocol and study milestones for reporting to the TGA. In addition, a rationale on how this study will further inform the area of important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' should also be provided. The GPRMP should be updated to reflect the addition of this study to the pharmacovigilance plan and provided to the OPR.
- The sponsor subsequently provided a final protocol and reporting period to the OPR. A rationale on how this study will further inform the area of important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' was provided to, and accepted by the OPR. The ASA was updated to reflect the regulatory imposition to include this study as part of the pharmacovigilance plan – this was accepted by the OPR.

Risk minimisation activities

- Consider adding the precaution from the SmPC (*Limitations of the clinical data*) to the precautions section of the proposed Australian PI to clearly inform prescribers that the available data does not support the use of Zinforo in CAP due to MRSA (see SmPC, page 4 [not in this AusPAR]).
- In addition, consider aligning the '*In vivo/in vitro susceptibility*' section of the proposed Australian PI with the relevant section from the SmPC (*Clinical efficacy against specific*

pathogens section), to further guide and clearly inform prescribers of the susceptible pathogens Zinforo has been demonstrated against.

- The recommended added precaution above should be assigned in the RMP to the areas of Important missing information 'Potential for suboptimal dosing in patients with more severe systemic upset' and 'Immunocompromised population'.
- The sponsor subsequently addressed these issues (refer Response from sponsor section below) – this was acceptable to the OPR.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality and pharmaceutical aspects of the submission was evaluated by Pharmaceutical Chemistry Evaluation (PCE) section and was considered by the PSC at its 146th meeting in July 2012. The PSC endorses all the issues raised by the TGA evaluator. In particular, the PSC supports the questions on the limits for impurities in the drug substance and degradants in the finished product specifications. The PSC agrees that the population pharmacokinetic analysis was well executed and a thoughtful and biologically plausible approach was undertaken. However, the PSC considered the importing of the non-compartmental analysis values for clearance (CL) for the haemodialysis patients into the bigger population group an oddity and an unusual practice in the population pharmacokinetic analysis. The advice from the PSC is that the pharmacokinetic/pharmacodynamic simulations were robust and give a clear indication that the dosing recommended is likely to achieve its therapeutic targets. The PSC noted that the manufacture of the two constituents involves an unusual number of aseptic operations. The PSC acknowledges that although these operations are carried out in closed systems, there was an increased potential for compromising the assurance of sterility in every vial of every batch. The applicant has since provided responses to questions raised by the TGA evaluator and additional matters raised by the PSC.

Endotoxin and microbiology aspects of the submission have been cleared.

There are now no objections in respect of Chemistry, Manufacturing and Controls to registration of Zinforo powder for injection, although this was at the time of this Overview, subject to resolution of a number of issues relating to PI amendments and GMP clearance.

Nonclinical

The nonclinical evaluator commented that the nonclinical studies are comprehensive and of high quality and were performed by reliable laboratories. The crucial toxicological studies were performed to GLP standard. The studies showed that ceftaroline bound most penicillin binding proteins (PBPs) from *Staphylococcus aureus* and *Streptococcus pneumoniae* strains, with an affinity comparable to or higher than comparator antibiotics; the studies also showed the bactericidal activity of ceftaroline towards a range of Gram-negative and -positive bacteria, under both *in vitro* and *in vivo* conditions. Ceftaroline showed similar or greater effectiveness than linezolid and vancomycin in treating bacterial species and strains that are frequently implicated in the proposed clinical indications for ceftaroline therapy. The evaluator is of the view that the combination of primary pharmacology studies and demonstrations of ceftaroline's bactericidal efficacy in both *in vitro* and *in vivo* assays supports its use for the proposed clinical indications. With

the exception of antibiotic-associated diarrhoea, no clinically relevant hazards were identified in the secondary pharmacodynamics and safety pharmacology studies conducted at ceftaroline concentrations approximating expected clinical plasma levels. Repeat-dose toxicity studies identified the kidney as the major target organ. Ceftaroline/ceftaroline fosamil is not considered to pose a genotoxic or carcinogenic hazard. The lack of significant effects of the test article on embryofetal development support its proposed placement in Pregnancy Category B1. Two of the seven impurities are not adequately qualified in nonclinical toxicity studies due to low exposure ratios but may be acceptable on clinical grounds due to the short period of patient treatment. Aside from the lack of adequate toxicological qualification of two impurities, the dossier of studies had no major deficiencies.

There are no objections from nonclinical perspective to the registration of the product and a number of amendments to the PI were recommended.

Clinical

Clinical pharmacology

The studies (pharmacokinetic/pharmacodynamic) submitted and evaluated include

- Five PK studies in healthy subjects (Studies P903-13, P903-01, P903-17, P903-20, and CXL-PK-01)
- Five PK studies assessing the effects of intrinsic factors (Studies P903-02, P903-04, P903-18, P903-15, and Study 903-11)
- Eight population pharmacokinetic (PPK) studies (Studies P903-HP-001, P903-HP-002, P903-HP-003, 00174-1, 00174-2, 00174-3, 00174-4, and 00174-5)
- One thorough QT study (Study P903-05)
- One study evaluating the effect of ceftaroline on enteric bacteria (Study P903-14)
- Five simulation studies using the models derived from the PPK studies (Studies 00174-6, 00174-7, 00174-8, and 00174-9)
- One study entitled "Technical Report: Supplementary target attainment analysis for patients with infection of cSSTI and CAP".

The clinical evaluator considers that the pharmacokinetics (PK) of ceftaroline fosamil were adequately characterised in adult subjects in the submitted PK studies. Ceftaroline fosamil (prodrug) is converted into the active ceftaroline in plasma. There was dose proportionality for ceftaroline C_{max} and AUC across the studied dose range (50-1000 mg). Ceftaroline and its metabolites are primarily eliminated by kidneys. Mean (SD) total recovery of intravenously administered ceftaroline fosamil is 93.4% (3.1%), with recovery from urine of 87.5% (3.9%) and faeces of 5.95 (2.93%). The mean percent of dose excreted in urine as ceftaroline is approximately 65%. Systemic exposure to ceftaroline prodrug and ceftaroline M-1, as determined by AUC, is about 2.5% and 20%, respectively, of the systemic exposure of ceftaroline. The mean steady state volume of distribution of ceftaroline in healthy adult males (n=6) following a single 600mg IV dose was 20.1 l. The half life of ceftaroline in healthy adult is *around 2.5 hour*.

In healthy elderly subjects (age \geq 65 years) ceftaroline C_{max} was similar to that for healthy young subjects but AUC was increased by 33% in the elderly group and ceftaroline clearance was decreased by 32%. In adolescent subjects clearance was increased to 14 L/h.

In subjects with moderate renal impairment, there was an around 10% increase in C_{max} and 50% increase in AUC of ceftaroline. In severe renal failure the C_{max} was increased by around 21%, AUC increased by 115%, $t_{1/2}$ increased by 67%, and clearance decreased by 53%. Clearance of ceftaroline was decreased by 63% in ESRD, by 50% with pre-dialysis administration, and by 90% with post-dialysis administration. In patients with moderate renal impairment, there was markedly increased exposure to ceftaroline M-1 with a doubling of C_{max} and tripling of AUC. In severe renal failure, ceftaroline M-1 C_{max} was increased by 120%, AUC increased by 300%, $T_{1/2}$ increased by 60%, and clearance decreased by 74%. Dose adjustments are recommended for patients with moderate renal impairment. There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment ($CrCL \leq 30$ ml/min) and ESRD, including patients undergoing haemodialysis. The PK of ceftaroline in patients with hepatic impairment have not been established.

In population PK (PPK) studies, the main covariate influencing the renal clearance of ceftaroline was $CrCl$ and the main influence on volume of distribution was body weight. The simulations predicted that in mild renal impairment, no dosage adjustment was necessary; in moderate renal impairment, the dose should be adjusted to 400 mg q12h; and in severe renal impairment, no formal dosage adjustment was proposed, but dose adjustment to 300 mg q12h may be adequate.

No clinical drug-drug interaction studies have been conducted with ceftaroline. No significant QT prolongation effect of ceftaroline 1500 mg was detected in the QT study.

Clinical efficacy

Two Phase II (Studies P903-03 and P903-19) and two Phase III studies (Studies P903-06 and P903-07) were provided to support the indication of cSSTI. For the indication of CAP, two Phase III studies were submitted (Studies P903-08 and P903-09).

Treatment of complicated skin and soft tissue infections (cSSTI)

Phase II studies: Two Phase II studies, Study P903-03 and P903-19 were provided, and these studies were not powered for hypothesis tests.

Study P903-03 was a Phase II multicentre, randomised, observer blinded study to assess the safety and efficacy of ceftaroline fosamil compared with standard therapy in adults with cSSTI. The study treatments were IV ceftaroline 600 mg q12h. The comparator was IV vancomycin 1 g q12h, with or without adjunctive IV aztreonam. Treatment duration was 7-14 days based on response. The primary efficacy endpoint was clinical response at Test of Cure (TOC) visit (8-14 days post therapy). Secondary efficacy endpoints include clinical response at EOT (End of Treatment) visit, microbiological response at TOC, clinical and microbiological response at TOC in the subgroup with MRSA, relapse at LFU (Later Follow Up) visit, and re-infection or recurrence at LFU. A total of 67 subjects randomised to ceftaroline and 33 to comparator, and 59 (88.1%) subjects in the ceftaroline group and 26 (78.8%) in the comparator group completed the study. For the primary efficacy endpoint, in the clinical modified intention to treat (cMITT) population, the cure rate (95% CI) was 88.1% (77.8% to 94.7%) in the ceftaroline group and was 81.3% (63.6% to 92.8%) in the comparator group.

Study P903-19 was a Phase II, multicentre, randomised, open-label, parallel group, and comparator-controlled study conducted in adults with cSSTI. The study treatment was IM Ceftaroline fosamil 600 mg q12h and the comparator was IV Linezolid 600 mg q12h. Aztreonam may have been started with linezolid or up to 72 hours after the first dose of linezolid if a mixed Gram-positive and Gram-negative infection been indicated or suspected at baseline. Treatment duration was 5 -14 days.

A total of 103 subjects received ceftaroline and 47 subjects received the comparator (2:1 ratio). The MITT population included 98 subjects in the ceftaroline group and 45 in the comparator. The cMITT population included 97 (94.2%) subjects in the ceftaroline group and 44 (93.6%) in the comparator. The microbiological modified intention to treat (mMITT) population included 77 (74.8%) subjects in the ceftaroline group and 38 (80.9%) in the comparator. The CE population included 86 (83.5%) subjects in the ceftaroline group and 39 (83.0%) in the comparator.

The treatment groups were similar in demographic, baseline characteristics and clinical features/severity. A lower proportion of subjects in the ceftaroline group had recent trauma and a higher proportion had diabetes mellitus. The lesions were similar in location and descriptive features. A high proportion of the isolates were MRSA, with a slightly higher proportion in the ceftaroline group: 61.0% isolates in the ceftaroline group compared with 55.3% isolates in the comparator group.

Primary efficacy analysis: the clinical cure rate at TOC for the MITT population was 84.7% (76.0% -91.2%) for ceftaroline and 88.9% (75.9%-96.3%) for comparator. There were too few subjects to enable subgroup comparisons.

Results for other efficacy outcomes: for the cMITT population, the clinical cure rate at TOC was 4.5% in ceftaroline group and 88.6% in comparator group. For *Staphylococcus aureus* clinical cure rates were slightly higher in the comparator group. For MITT population at EOT visit, the clinical cure rate was 87.8% for ceftaroline and 93.3% for comparator. One subject in each group experienced a clinical relapse at LFU. In the mMITT population, 85.7% of the subjects in ceftaroline group and 89.5% in comparator group had a favourable microbiological response at TOC. Per pathogen microbiological response was similar for the two groups but there were too few bacterial isolates to enable proper comparison.

Phase III studies: two Phase II studies, Study P903-06 and P903-07 were provided.

Study P903-06 was a Phase III multicentre, randomised, double blind, controlled, parallel group, non-inferiority study. The efficacy and safety of ceftaroline fosamil was compared to vancomycin plus aztreonam in adult subjects with cSSTI.

The inclusion/exclusion criteria were detailed in the clinical evaluation report (CER). The majority of patients had deep/extensive cellulitis or a major abscess. Other infections included wound infections (surgical or traumatic), infected bites, burns or ulcers or any lower extremity infections in patients with either pre-existing diabetes mellitus (DM) or peripheral vascular disease (PVD). The key exclusion criteria included necrotizing fasciitis, peri-rectal abscess, third degree and extensive burns, diabetic foot ulcer or foot ulcer associated with PVD and immunosuppressed patients.

The treatments were IV Ceftaroline fosamil 600 mg q12h (dose modified to 400 mg in moderate renal failure) plus placebo q12h. The comparator treatments were IV vancomycin 1 g q12h (dose modified in moderate renal failure) and IV aztreonam 1 g q12h. Treatment duration was 5-7 days.

The primary efficacy endpoint was clinical cure rate at TOC visit in the CE and cMITT populations. The secondary efficacy endpoints were the same as for Study P903-03 with the addition of Clinical Response at TOC visit. The criteria for treatment failure also included:

- Treatment-limiting AE leading to study drug discontinuation, when subject required alternative antimicrobial therapy to treat the cSSTI, including oral step-down therapy
- Diagnosis of osteomyelitis 8 or more days after randomisation.

The Intent-to-Treat (ITT) population consisted of all randomized subjects. The MITT population consisted of all randomised subjects who received any amount of study drug.

The cMITT population consisted of all subjects in the MITT population who met the minimal criteria for a cSSTI. The mMITT population consisted of all subjects in the cMITT population who had at least one bacterial pathogen identified from a blood culture or from a culture of an adequate microbiological sample obtained from the cSSTI site at baseline. The CE population was a subset of the cMITT population that include subjects who received at least the pre-specified minimum amount of the intended dose and duration of study drug, for whom sufficient data regarding the cSSTI site was available to assess the outcome and for whom there were no confounding factors that interfered with the outcome assessment.

The rationale for the 10% non-inferiority margin and sample size estimation were discussed in the CER. A total of 353 randomised to ceftaroline and 349 to the comparator (1:1). In the cMITT population there were 345 subjects in the ceftaroline group and 344 in the comparator. In the mMITT population there were 271 subjects in the ceftaroline group and 263 in the comparator. A total of 325 subjects in the ceftaroline group and 315 in the comparator group completed the study.

Baseline data: the treatment groups were similar in past medical history, the clinical characteristic of the infection. The infection sites were of similar mean size and the types of infection were similarly distributed for the two treatment groups. The infections were predominantly *Staphylococcal*, with around 30% being MRSA. Other than the *Enterococcus faecalis* isolates, the Gram positive isolates were susceptible to ceftaroline but the Gram negative organisms were predominantly not susceptible¹³ Disease severity at baseline was similar for the two groups. Additional systemic antibacterial treatment was required by 7.1% subjects in the ceftaroline group and 7.5% in the comparator.

Results of primary efficacy analysis: Non-inferiority was demonstrated for the primary efficacy endpoint. In the CE population, clinical cure rate was 91.1% for the ceftaroline group and 93.3% for the comparator group with difference of -2.2% (95% CI: -6.6% to 2.1%). For the MITT population, clinical cure rate was 86.6% for the ceftaroline group and 85.6% for the comparator group with difference of 1.0% (95% CI: -4.2% to 6.2%).

Results for other efficacy endpoints: for the mMITT population, a favourable microbiological response at TOC was recorded for 86.3% subjects in the ceftaroline group and 83.7% in the comparator, difference (95% CI) 2.7% (-3.4% to 8.9). Clinical cure at EOT visit in the MITT population was recorded for 91.7% subjects in the ceftaroline group and 90.2% in the comparator, difference (95% CI) 1.5% (-2.8% to 5.9%). Clinical response by baseline pathogen in the ME population was similar for the two treatment groups for Gram positive organisms but there was a poorer response in the ceftaroline group for Gram negative organisms. Three subjects in each treatment group experienced a clinical relapse at LFU after having been assessed as cured at TOC.

Study P903-07 was a Phase III multicentre, randomised, double blind, active controlled, non-inferiority study. The efficacy and safety of ceftaroline fosamil was compared to vancomycin plus aztreonam in adult subjects with cSSTI. The design was identical to Study P903-06.

A total of 694 subjects were randomized: 348 to ceftaroline and 346 to comparator. CE population included 294 subjects in ceftaroline group and 292 in the comparator group. cMITT population included 341 subjects in the ceftaroline group and 337 in the comparator group. In the mMITT population, there were 269 (77.3%) subjects in the ceftaroline group and 259 (74.9%) in the comparator.

¹³ Sponsor clarification: "In the pooled ME population the majority of Gram-negative organisms were susceptible to ceftaroline with the exception of *Pseudomonas aeruginosa* (see PI "Pharmacology/Susceptibility testing" section) and *Proteus mirabilis*."

Baseline data: there were 62.5% males 37.5% females and the age range was 18 to 96 years. The two groups were similar in past medical history, signs and symptoms of cSSTI, lesion size, type and site of infection and distribution of pathogens. Around 80% of the isolated were *Staphylococcus aureus* with 30% being MRSA. The Gram positive organisms were susceptible to ceftaroline and vancomycin but the Gram negative organisms, with the exception of *Escherichia coli*, were not susceptible to ceftaroline.¹⁴

Results of primary efficacy analysis: non-inferiority was demonstrated for the primary efficacy endpoint. The clinical cure rate was 92.2% for the ceftaroline group and 92.1% for the comparator group in the CE population, with difference of 0.1% (-4.4% to 4.5%). For the MITT population, clinical cure rate was 85.1% for ceftaroline group and 85.5% for the comparator group with the difference of -0.4% (-5.8% to 5.0%). Clinical cure rates were slightly better for subjects >75 years age: 83.3% in the ceftaroline group and 78.9% in the comparator group and the difference was 4.4% (-19.5% to 30.0%).

Results for other efficacy endpoints: for the mMITT population, a favourable microbiological response at TOC was recorded for 233 (86.6%) subjects in the ceftaroline group and 229 (88.4%) in the comparator, difference was -1.8% (-7.5% to 3.9%). Clinical cure at EOT visit in the MITT population was recorded for 304 (88.9%) subjects in the ceftaroline group and 302 (89.3%) in the comparator, the difference was -0.5% (-5.2% to 4.3%). Clinical response by baseline pathogen was similar for the two groups for Gram positive organisms but there was a poorer response in the ceftaroline group for Gram negative organisms. Three subjects in the ceftaroline group and two in the comparator experienced a clinical relapse at LFU after having been assessed as cured at TOC.

Pooled efficacy analyses: Study P903-06 and P903-07 were pooled, and the following results were obtained from a pooled efficacy analysis in the MITT population:

- Clinical cure at TOC was reported for 85.9% subjects in ceftaroline group and 85.5% in the comparator group; Weighted Difference (95% CI) 0.3% (-3.4% to 4.0%)
- Clinical cure at EOT was reported for 90.3% subjects in ceftaroline group and 89.8% in the comparator group; Weighted Difference (95% CI) 0.6% (-2.6% to 3.8%)
- Clinical cure at TOC for subjects with MSSA (mMITT population) was reported for 221 (90.2%) subjects with ceftaroline and 233 (90.3%) with comparator; Weighted Difference (95% CI) -0.1% (-5.5% to 5.2%)
- Clinical cure at TOC for subjects with MRSA (mMITT population) was reported for 155 (86.6%) subjects with ceftaroline and 124 (82.1%) with comparator; Weighted Difference (95% CI) 4.4% (-3.4% to 12.6%)
- Clinical cure at TOC for subjects with MRSA (mMITT population) was reported for 429 (87.7%) subjects with ceftaroline and 420 (86.6%) with comparator; Weighted Difference (95% CI) 1.1 (-3.1 to 5.4).

Treatment of Community-acquired Pneumonia (CAP)

Phase III studies (P903-08 and P903-09)

Study P903-08 was a Phase III, multicentre, randomised, double blind, comparator controlled, non-inferiority study conducted in adults with community acquired pneumonia (CAP). The study treatments were IV ceftaroline fosamil 600 mg q12h (reduced to two doses of 200 mg q12h if CrCl >30 mL/min and ≤50 mL/min). The comparator was IV ceftriaxone 1 g q24h, with saline placebo to maintain blinding. Two

¹⁴ Sponsor clarification: "In the pooled ME population the majority of Gram-negative organisms were susceptible to ceftaroline with the exception of *Pseudomonas aeruginosa* (see PI "Pharmacology/Susceptibility testing" section) and *Proteus mirabilis*."

doses of oral clarithromycin, 500 mg q12h, were administered in both groups as adjunctive treatment. The treatment duration was 5-7 days.

Inclusion and exclusion criteria were detailed in the CER. Subjects had to have pneumonia as confirmed by chest x-ray, plus certain signs and symptoms of disease. In addition, the inclusion criteria required subjects to have PORT (Pneumonia Outcomes Research Trial) scores of either III or IV¹⁵. It is important to note that subjects infected with/or likely to be infected with MRSA were not permitted to be enrolled because the comparator agent ceftriaxone is not active against this MRSA. The other key exclusion criteria included the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT Risk Class V, and/or CAP requiring ventilation/ intensive care.

The primary efficacy endpoint was the clinical cure rate at TOC in the CE and MITTE Populations. The secondary efficacy endpoints, clinical/radiological/microbiological outcome categories and sample size estimation were detailed in the CER.

The trial was designed to evaluate whether ceftaroline was non-inferior to ceftriaxone using an endpoint of clinical cure at the TOC visit with a non-inferiority margin of 10%. A total of 305 subjects were randomised to ceftaroline and 309 to ceftriaxone (1:1). A total of 277 subjects in the ceftaroline group and 283 in the ceftriaxone completed the study.

The definition of the analysis populations were as follows:

- The ITT population consisted of all randomised subjects.
- The MITT population consisted of all randomized subjects who received any amount of study drug. The MITT population was used for safety analyses.
- The MITTE population consisted of all subjects in PORT Risk Class III or IV in the MITT population.
- The mMITT population consisted of all subjects in the MITT population who met the minimal disease criteria for CABP, whose PORT Risk Class was II, III or IV, and who had at least one typical bacterial organism consistent with a CABP pathogen identified from an appropriate microbiological specimen (for example, blood, sputum or pleural fluid).
- The mMITTE population consisted of all subjects with a PORT Risk Class of III or IV in the mMITT population.
- The CE population consisted of all subjects in the MITTE population who also met the minimal disease criteria for CABP and for whom sufficient information regarding the CAP was available to determine the subject's outcome.

The number of subjects in each treatment groups in these analysis populations is detailed in the CER. The two groups were similar in demographic and baseline characteristics. Structural lung disease, prior pneumonia and alcohol abuse were more common in the ceftaroline group. Prior respiratory signs and symptoms were also slightly more common in the ceftaroline group. The signs and symptoms of CAP were similar for the two groups at baseline. Staphylococcus aureus isolates were less common in ceftaroline group (13.3% versus 17.5%). Aerobic Gram negative isolates were more common in ceftaroline group (58.7% versus 55.0%). The Staphylococcal isolates appear to have been sensitive to ceftaroline but relatively resistant to ceftriaxone. The MICs for ceftriaxone of the Staphylococcal isolates were in the range 2 to 4 µg/mL, and the minimal inhibitory

¹⁵ The pneumonia severity index [PSI] or PORT Score is a clinical prediction rule that medical practitioners can use to calculate the probability of morbidity and mortality among patients with community acquired pneumonia. The severity of the disease symptoms increases with the score from I-V.

concentration required to inhibit the growth of 90% of organisms (MIC90) was 4 µg/mL. Systemic antibiotics were received in the 96 hours prior to randomisation by 143 (47.8%) subjects in the ceftaroline group and 146 (47.6%) in the ceftriaxone. Additional systemic antibiotics were received from randomization to TOC by 43 (14.8%) subjects in the ceftaroline group and 57 (19.0%) in the ceftriaxone.

Results for the primary efficacy outcomes: non-inferiority was demonstrated for the primary efficacy endpoint. In the CE population, clinical cure rate was 86.6% in the ceftaroline group and 78.2% in the ceftriaxone group; difference was 8.4% (1.4% to 15.4%). In the MITTE population, clinical cure rate was 83.8% in the ceftaroline group and 77.7% in the ceftriaxone, difference was 6.2% (-0.2% to 12.6%). The clinical cure rate for ceftaroline was not adversely affected by demographic or baseline characteristics.

Results for other efficacy outcomes: Clinical response at EOT was greater in the ceftaroline group in the MITTE and CE populations. In the MITTE population, clinical cure at EOT was recorded for 86.9% subjects in the ceftaroline group and 80.7% in the ceftriaxone group, difference in rates was 6.3% (0.3% to 12.3%). There was no significant difference in microbiological success rate at TOC in the mMITT, mMITTE and ME populations. In the mMITT population, clinical cure at TOC was recorded for 88.0% subjects in the ceftaroline group and 79.3% in the ceftriaxone group, difference in rates 8.7% (-3.1% to 20.5%). There was no significant difference in overall success rate at TOC in the MITTE population, but ceftaroline had a higher success rate in the CE population. In the CE population, for overall success, cure at TOC was recorded for 86.6% subjects in the ceftaroline group and 78.2% in the ceftriaxone group; difference in rates 8.4% (1.4% to 15.4%). Clinical/microbiological response by pathogen at TOC in the ME population was better in the ceftaroline group for *Staphylococcus aureus* and *Streptococcus pneumoniae*. Clinical relapse at LFU occurred in 3 (1.2%) subjects in the ceftaroline group and 3 (1.3%) in the ceftriaxone group. Median time to defervescence of fever for the MITTE population was 2.0 days (95% CI: 2.0 to 3.0) for both groups. Median time to resolution of hypoxia was 2.0 days (95% CI: 2.0 to 3.0) in the ceftaroline group and 3.0 days (2.0 to 3.0) in the ceftriaxone group. In the MITTE population, the 30 day mortality rate was 1.4% in the ceftaroline group and 1.7% in the ceftriaxone group. The total mortality rate was 1.7% in the ceftaroline group and 1.7% in the ceftriaxone group. There were no subjects in the MITTE population with microbiological re-infection/ recurrence at LFU.

Study P903-09 was a Phase III, multicentre, randomised, double blind, comparator controlled (ceftaroline versus ceftriaxone), non-inferiority study in subjects with CAP. The study design was similar to Study P903-08, the main difference being the use of clarithromycin as adjuvant treatment in Study P903-08. The efficacy endpoints, analysis populations and statistical methods were the same as for Study P903-08.

The study treatments were IV ceftaroline fosamil 600 mg q12h (reduced to 400 mg q12h if CrCl >30 mL/min and ≤50 mL/min). The comparator treatments were IV ceftriaxone 1 g q24h, with saline placebo to maintain blinding. Two doses of oral clarithromycin, 500 mg q12h, were administered in both groups as adjunctive treatment. The treatment duration was for 5 to 7 days.

The sample size was based on a point estimate of the overall success rate of 90% in the CE population in both groups. The non-inferiority margin was 10% which was to ensure that ceftaroline maintained a significant fraction of the treatment effect of antibiotics for CAP over a putative placebo.

A total of 317 subjects randomised to ceftaroline and 310 to ceftriaxone. The two groups were similar in demographic and baseline characteristics. A higher proportion of subjects in the ceftaroline group had a relevant prior medical history: 147 (50.9%) subjects compared with 120 (44.0%). Respiratory signs/symptoms and disease severity at baseline were similar for the two groups. Of the bacterial isolates, the most commonly isolates

were: *Streptococcus pneumoniae* 46.1%, *Staphylococcus aureus* 17.4%, and *Haemophilus influenzae* 16.3%. Fifteen subjects in the ceftaroline group and eleven in the ceftriaxone had positive blood cultures. Systemic antibacterial treatment prior to randomisation was received by 35.9% subjects in the ceftaroline group and 42.3% in the ceftriaxone group. Additional systemic antibiotics from randomisation to TOC were received by 16.3% subjects in the ceftaroline group and 22.0% in the ceftriaxone group. The *Staphylococcus aureus* isolates had greater susceptibility to ceftaroline than ceftriaxone.

Results for the primary efficacy outcomes: non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone. In the CE population, clinical cure was recorded for 193 (82.1%) subjects in the ceftaroline group and 166 (77.2%) in the ceftriaxone, difference in rates 4.9% (95% CI: -2.5% -12.5%). In the MITTE population, clinical cure was recorded for 235 (81.3%) subjects in the ceftaroline group and 206 (75.5%) in the ceftriaxone, difference in rates was 5.9% (-1.0% to 12.7%). The cure rate for ceftaroline was not adversely affected by demographic or baseline characteristics.

Results for other efficacy outcomes: Clinical response at EOT was greater in the ceftaroline group in the MITTE and CE populations. There was no significant difference in microbiological success rate at TOC in the mMITT, mMITTE and ME populations. In the mMITT population, favourable response at TOC was recorded for 81.8% subjects in the ceftaroline group and 81.4% in the ceftriaxone, difference in rates was 0.4% (-10.5% to 11.3%). There was no significant difference in overall success rate at TOC in the MITTE or CE populations. In the MITTE population, for overall success, cure at TOC was recorded for 81.0% subjects in the ceftaroline group and 75.5% in the ceftriaxone group, difference in rates was 5.5% (-1.3% -12.4%). Clinical response by pathogen at TOC in the ME population was better in the ceftaroline group for *Staphylococcus aureus* and *Streptococcus pneumoniae*, and microbiological response was better for *Streptococcus pneumoniae*. Clinical relapse at LFU occurred in five (2.1%) subjects in the ceftaroline group and two (1.0%) in the ceftriaxone group. Median time to defervescence of fever for the MITTE population was 2.0 (2.0 - 2.0) for the ceftaroline group and 2.0 (2.0 -3.0) days for the ceftriaxone group. Median time to resolution of hypoxia was 2.0 (2.0-3.0) days for both groups. In the MITTE population, the 30 day mortality rate was 2.8% in the ceftaroline group and 1.6% in the ceftriaxone group. The total mortality rate was 3.1% in the ceftaroline group and 1.7% in the ceftriaxone group. There were no subjects in the MITTE population with microbiological reinfection/recurrence at LFU. No subject in the ceftaroline group had a pathogen with decreasing ceftaroline susceptibility.

Pooled efficacy analysis

A pooled efficacy analysis was conducted for Study P903-08 and Study P903-09. The results showed that in the MITTE population, ceftaroline was superior to ceftriaxone for clinical response at TOC: 82.6% subjects in the ceftaroline group compared with 76.6% in the ceftriaxone group, with weighted difference being 6.0% (1.4%-10.7%). In the mMITTE population for Gram positive organisms, ceftaroline was superior to ceftriaxone for clinical response at TOC: 83.7% subjects in the ceftaroline group compared with 66.0% in the ceftriaxone group and the weighted difference was 17.9% (5.5% - 29.8%); but there was no difference between the two treatments for Gram negative organisms: 83.3% subjects in the ceftaroline group compared with 83.5% in the ceftriaxone group with the weighted difference being -0.2% (-11.4% -10.8%). Response rates were not influenced by demographic factors, in confirmation of the individual study results.

It is noted that there were insufficient subjects with MRSA infection to perform a comparison between the two treatment groups.

Clinical safety

There were a total of 1470 subjects exposed to ceftaroline fosamil in Phase II and Phase III trials during the development program. This included 613 with CAP and 857 with cSSTI. There were no subjects aged less than 18 years included in the Phase II and III trials. There were 402 subjects age 65 years or more, including 188 subjects aged 75 years or more. There were 117 subjects with creatinine clearance >30 and ≤50 mL/min and 15 subjects with creatinine clearance ≤30 mL/min. There were 169 subjects with hepatic impairment and 287 with cardiac impairment.

TEAEs were reported in around 60% of subjects and occurred at a similar rate to comparator treatment. Headache occurred in up to 16% of subjects, nausea in 12% and diarrhoea in 5%. Urine discolouration and odour occurred at the 600 mg q12h dosing level. Some subjects reported body odour. Injection site AEs occurred in approximately 40% of subjects. Ceftaroline did not appear to be associated with QT prolongation in either the Thorough QT study or in the clinical studies. Ceftaroline did not appear to be associated with seizures or hepatobiliary dysfunction.

SAEs were uncommon and were not usually attributable to the study treatment. In Study P903-07, anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects and were attributed to ceftaroline. Death was uncommon and none were attributed to study treatment.

Ceftaroline appeared to be well tolerated with up to 5% of subjects discontinuing because of AEs which were not usually attributed to study treatment. Up to 21% of subjects developed a positive direct Coomb's test during treatment. However, there was no increased incidence of haemolytic anaemia.

The Important identified risks are clostridium difficile colitis, hypersensitivity and anaphylaxis. The Important potential risks include bacterial resistance development, convulsion / seizures, drug-induced liver injury (based on observance of transient increases in liver enzyme levels), haemolytic anaemia (based on observance of positive Coombs' test), renal impairment, including potential drug interactions with nephrotoxic agents (based on class effects and observance of increased serum creatinine levels). Clinical study experience with ceftaroline in patients with severe renal impairment and ESRD is limited.

Australian antibiotic resistance surveillance data

An updated 2010 Australian specific antibiotic resistance data is provided in the Australian surveillance report. The activity of ceftaroline tested against contemporary clinical isolates collected in Australia from January to December 2010 was provided. A total of 1,523 bacterial isolates from six medical centres were cultured in 2010 and tested for susceptibility to ceftaroline and comparator agents by Clinical Laboratory and Standards Institute (CLSI) reference MIC methods. *Staphylococcus* spp. including MRSA appeared to be susceptible to ceftaroline. Ceftaroline also showed potent activity against streptococci, including *S. pneumoniae* and Gram-negative pathogens (*H. influenzae*, *H. parainfluenzae* and *M. catarrhalis*) associated with community-acquired respiratory tract infections. Furthermore, wild-type strains of Enterobacteriaceae (non-ESBL¹⁶-producers and non-AmpC¹⁷-hyperproducers) were often very susceptible to ceftaroline.

A surveillance report of isolates from the Asia Pacific region, including Australia and New Zealand, was provided as Ceftaroline-M1-002-09-AZ-03. This report indicated sensitivity

¹⁶ ESBL=extended-spectrum beta-lactamase; an enzyme capable of hydrolysing penicillins and cephalosporins.

¹⁷ AmpC=AmpC β-lactamases are clinically important cephalosporinases encoded on the chromosome of many Enterobacteriaceae and a few other organisms where they mediate resistance to cephalothin, cefazolin, cefoxitin, most penicillins, and β-lactamase inhibitor/β-lactam combinations.

of *Staphylococcus aureus* and *Streptococcus pneumonia* isolates from the region and also Australia. Coagulase negative *Staphylococcus* (CoNS) isolates also showed good sensitivity to ceftaroline but *Enterococcus* isolates were all resistant.

Delegate's comment and issues

Treatment of cSSTI

The non-inferiority of ceftaroline (600 mg IV q12h) versus vancomycin was demonstrated in Study P903-06 with regards to the primary efficacy endpoint. There appeared to be a poorer response for Gram negative organisms. The non-inferiority was also demonstrated for ceftaroline in comparison with vancomycin in Study P903-07 with regards to the primary efficacy endpoint. In Study P903-07, there also appeared to be a poorer response for Gram negative organisms. The pooled analysis of the two studies supported the efficacy of ceftaroline for the treatment of cSSTI due to MRSA. The evaluator noted that the comparators used in the two Phase III studies would not normally be first line treatment for cSSTI in Australia. Such infections would normally be treated with flucloxacillin as a first line agent. Vancomycin would be used as a second line agent and first-line for patients with penicillin allergy. Linezolid would normally be reserved as a third line agent. Aztreonam is not usually used for the indication of cSSTI in Australia but is acceptable treatment for cSSTI resulting from Gram negative organisms.

Treatment of CAP

With regards to the pre-defined primary efficacy endpoint, non-inferiority was demonstrated for ceftaroline (600 mg IV q12h) in comparison with ceftriaxone in Study P903-08 in which clarithromycin was used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline group for *Staphylococcus aureus* and *Streptococcus pneumoniae*. In Study P903-09, for the primary efficacy endpoint, non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone, when clarithromycin was not used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline group for *Staphylococcus aureus* and *Streptococcus pneumoniae*. It is noted that the comparator, ceftriaxone, would not normally be the first line treatment for CAP in Australia. Such infections would normally be treated with penicillin as a first line agent, unless the patient's condition was severe. Ceftriaxone is commonly used for hospital acquired pneumonia in the Australian setting. But ceftriaxone is considered as an acceptable treatment for CAP.

Although the comparators used in the trials were not the first line treatment for cSSTI or CAP in Australia, it is considered that the comparators do provide an acceptable standard of care for these conditions. For the treatment of cSSTI, efficacy was demonstrated against infection caused by MRSA and also penicillin resistant strains of *Streptococcus pneumoniae*. For the treatment of CAP, there were insufficient subjects with MRSA to perform a comparison.

The safety profile of ceftaroline is considered acceptable.

It should be noted that there are limitations with the submitted clinical data. For the treatment of CAP, there is no experience with ceftaroline in the treatment of CAP in the immune-compromised, in patients with severe sepsis and septic shock, patients with severe underlying lung disease, in those with PORT Risk Class V, and/or CAP requiring ventilation at presentation, in CAP infection due to MRSA or patients requiring intensive care. For the treatment of cSSTI, there is no experience with the immune-compromised, in patients with severe sepsis/septic shock, necrotizing fasciitis, peri-rectal abscess and patients with third degree and extensive burns. There is limited experience in treating patients with diabetic foot infections. Caution is advised when treating such patients.

Overall, the benefit-risk balance of ceftaroline, given the proposed usage, is considered favourable for the treatment in adults with cSSTI or CAP, providing the PI reflects accurately the available information and agreed RMP be implemented during post-marketing phase.

Product Information

PI has been reviewed by the evaluators from quality, nonclinical, clinical and RMP evaluation areas. In addition to the recommendations from these evaluators, it is recommended that the statements in the PI should be clear that although *in vitro* susceptibility data are available for some pathogens, the clinical significance for these is unknown. The activities of ceftaroline against specific pathogens are different between the treatment for CAP and the treatment for cSSTI and the description relating to these in the PI should be separated for the two clinical conditions. The PI documents approved by FDA and EMA are very clear in this area. Limitation of the clinical trial data should also be discussed in the PI. A draft PI incorporating recommended changes should be submitted with the sponsor's Pre-ACPM response. Further changes to the PI may be required after the ACPM discussion.

Risk management plan

The submitted GPRMP Version 2 with Addendum 1 (Australian Risk Minimisation Activities) has been review by the TGA's OPR and has been considered by the ACSOM. The ACSOM endorses the evaluator's recommendation that confirmation or strong suspicion of bacterial susceptibility prior to the initiation of Zinforo treatment is appropriate and practical. The committee noted that inclusion of the need for confirmation of bacterial susceptibility in the indication would be consistent with the increasing prevalence of formal antimicrobial stewardship programs in Australia. These programs specify which drugs to use first, as well as appropriate testing and criteria required to move to second and third line agents. ACSOM advised that it would not be appropriate to use ceftaroline fosamil as first line treatment and tighter wording in the indications will help reinforce this message. ACSOM questioned whether all prescribers would understand the term 'directed' in the proposed indications; and suggested that the wording 'proven or strongly suspected' might be less prone to misunderstanding than 'empirical or directed'.

ACSOM advised that there was insufficient detail available for members to provide any robust advice on the proposed bacterial resistance surveillance program. The committee endorsed the OPR's recommendations that the sponsor should provide a full protocol or detailed protocol synopsis for the Bacterial Resistance Surveillance Programme prior to marketing. ACSOM also stressed that the study should include Australian sites.

The OPR also requested that the sponsor to reclassifying the "Important other information-Potential for off-label use' as an Important potential risk and to add "Potential for suboptimal dosing in patients with more severe systemic upset" in the area of Important missing information.

See also *Pharmacovigilance Findings; Summary of Recommendations* above.

Risk-benefit analysis

Delegate considerations

Specific issues for ACPM advice

The advice from ACPM is requested, specifically with the following issues:

4. What is the ACPM's view with regards to the pre-defined primary efficacy endpoint used in the pivotal studies? Are these endpoints reflecting accurately the relevant clinical outcomes?
5. What is the ACPM's view with regards to the comparator treatments used in the pivotal trials?
6. Does ACPM endorse that the *Indications* statement should include tighter wordings, such as "*infections proven or strongly suspected to be caused by designated susceptible bacteria*"?
7. What is the ACPM's view in term of the overall risks/benefits balance of ceftaroline fosamil for the proposed indications?
8. Does ACPM like to make a general comment in relation to issues of antibiotics resistance?

Proposed action

Pending the advice from the ACPM, the Delegate proposed the registration approval for the use of Zinforo (ceftaroline fosamil) 600mg power for injection for the following indications:

Zinforo is indicated for the treatment of patients with the following infections proven or strongly suspected to be caused by designated susceptible bacteria:

- Complicated skin and soft tissue infections
- Community-acquired pneumonia

The recommended doses for adults are 600 mg every 12 hours by IV infusion over 60 minutes for 5-7 days for CAP or 5-14 days for cSSTI. Dose reductions are required for patients with renal impairment.

The finalisation of this application was subject to satisfactory negotiation of the PI and clearance of the GMP. The condition of registration should include the implementation of the GPRMP Version 2, dated 18 November 2011 with Addendum 1 – Australian Risk Minimization Activities, dated November 2011¹⁸, and any future updates to the RMP.

Response from Sponsor

AstraZeneca concurs with the clinical evaluator and the Delegate that the overall benefit:risk balance of Zinforo (ceftaroline fosamil) 600 mg powder for injection for the treatment of cSSTI and CAP is positive, and thus approval should be recommended. The positive benefit:risk balance of Zinforo in these two indications is further supported by the corresponding approvals in the United States (as Teflaro) in October 2010 and the European Union (as Zinforo) in August 2012.

The Delegate has provided comment on certain aspects of the evaluation within the "Request for ACPM Advice" including questions relating to: a modified indication, the pivotal efficacy and safety data (including primary endpoints, comparator treatments and overall risk/benefit balance) and antibiotic resistance. AstraZeneca's considerations of these issues are discussed further below.

Proposed indication

AstraZeneca accepts the following modified indication requested by the Delegate (and the RMP evaluator). The draft PI has been amended accordingly.

¹⁸ Note: "This was changed to Australian Specific Annex Edition 2 with the sponsor's RMP response to OPR."

Zinforo is indicated for the treatment of patients with the following infections proven or strongly suspected to be caused by designated susceptible bacteria:

- Complicated skin and soft tissue infections
- Community-acquired pneumonia

Zinforo is safe and efficacious in cSSTI and CAP

Efficacy and safety was demonstrated in two multinational, multicentre, randomised, double blinded, well controlled Phase III studies in adult patients for each of the indications being sought.

Study design

Overall design

The two cSSTI studies were identical in design, population, inclusion/exclusion criteria and dosing regimens. Both studies compared ceftaroline to vancomycin plus aztreonam for 5 to 14 days treatment (with potential for extension). The two CAP studies were also identical in design, population, inclusion/exclusion criteria and dosing regimens; with one exception (one study included a brief oral clarithromycin course in both arms). Both studies compared ceftaroline to ceftriaxone for 5 to 7 days treatment.

Choice of primary endpoint – clinical cure rate at test-of-cure (TOC)

The primary objective in all the Phase III studies was the demonstration of non-inferiority of ceftaroline to the comparator regimen (vancomycin/aztreonam for cSSTI; ceftriaxone for CAP) in the primary efficacy endpoint of clinical cure rate at test-of-cure (TOC) in the co-primary populations - clinically evaluable (CE for both) and modified intent-to-treat (MITT for cSSTI and MITT efficacy [MITTE] for CAP). The definition of clinical cure was defined either as total resolution of all signs and symptoms (of cSSTI or CAP) or improvement to such an extent that further antimicrobial therapy was not necessary. This is consistent with the definition recommended in the CPMP Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections¹⁹ which states that cure is usually defined as complete resolution of signs and symptoms but no requirement for further antibacterial therapy may additionally be used for some infections and uses some skin and soft tissue infections as an example. TOC is recognised as the most clinically relevant endpoint for assessing the treatment outcome for a patient in cSSTI as concluded at the EU workshop on antibacterials²⁰ which was an EU cross functional discussion held between regulators, academics and industry. It is also cited as the recommended primary endpoint in the draft addendum to the above CPMP guideline for cSSTI and CAP (EMA/CHMP/776609/2011)²¹.

Choice of comparators

Vancomycin and aztreonam were chosen as the active comparators for the cSSTI studies because of their acceptance in clinical practice as highly effective, standard-of-care therapies for cSSTI, and because of the need to cover methicillin resistant *Staphylococcus aureus* (MRSA). The use of vancomycin as a comparator due to MRSA coverage in cSSTI is further supported by the Australian Antibiotic Therapeutic Guidelines (version 14; 2010)

¹⁹ 2012 implementation; While not adopted by TGA at this point of time, the related concept paper is referred to on the TGA website within the EU guidelines section; CPMP/EWP/558/95 rev 2: guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. (final – issued 15 December 2011)

²⁰ EMA/257650/2011: Workshop on antibacterials. Report of the workshop. (17 March 2011)

²¹ EMA/CHMP/776609/2011: Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data (draft - issued 21 June 2012) Therapeutic Guidelines. Antibiotics, Version 14; 2010.

recommendations. Aztreonam was used in combination with vancomycin to provide empirical Gram negative coverage.

Ceftriaxone was chosen as the active comparator in the CAP studies due to its global acceptance as appropriate therapy for treatment of patients hospitalized with CAP. This is further supported by the recommendations in the Australian Antibiotic Therapeutic Guidelines for in-patient treatment of moderate-severe CAP. In addition, both agents belong to the same class to allow like-to-like comparisons.

While it is acknowledged that other antibiotic therapies are also recommended for use in these infections in Australia (for example flucloxacillin in cSSTI, and penicillins in CAP) they were not the most appropriate comparators taking into consideration the need to assess the broad activity of ceftaroline including MRSA and/or Gram negative coverage.

Both the Delegate and the clinical evaluator acknowledge that the comparators used in the cSSTI (vancomycin/aztreonam) and CAP (ceftriaxone) studies are considered as acceptable treatment options in Australia. As stated above, this is further supported by the Australian treatment guidelines, particularly taking into consideration the need for broad coverage including MRSA.

Patient selection / clinical trial limitations

AstraZeneca acknowledge the limitations of the pivotal clinical trials based on the patient inclusion/exclusion criteria, for example the exclusion of patients with suspected or confirmed MRSA in the CAP studies due to the lack of activity of the comparator (ceftriaxone) on this pathogen. The draft PI (not included in this AusPAR) already details many of the key inclusion and exclusion criteria within the *Clinical Trials* section, and this has now been expanded to include additional criteria in line with the Delegate and RMP evaluator recommendations.

Clinical efficacy

Both the Delegate and clinical evaluator accepted that non-inferiority of ceftaroline was demonstrated with regards to the clinical cure rate (primary endpoint) when compared to vancomycin/aztreonam (for cSSTI) and ceftriaxone (for CAP). Furthermore, there is convincing clinical and microbiological support for efficacy in treating cSSTI caused by *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Morganella morganii*. In the treatment of CAP, there is also compelling clinical and microbiological efficacy when caused by *S. pneumoniae*, *S. aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *K. pneumoniae*, and *E. coli*. The robustness of the conclusions of both clinical programs was demonstrated by analyses showing homogenous clinical responses across a variety of subgroups, including demographic and baseline characteristics, disease severity, and comorbid conditions.

Clinical safety

Analysis of pooled safety data in patients with either cSSTI or CAP demonstrated that the safety profile of ceftaroline was consistent with that of other cephalosporins and that ceftaroline was well-tolerated in the intended treatment populations. Subsequently, the Delegate concluded that “the safety profile of ceftaroline is considered acceptable”.

Positive benefit/risk profile

Microbiologically and pharmacologically, ceftaroline offers many benefits in the treatment of cSSTI and CAP. It is bactericidal with Gram-positive and non-extended-spectrum β -lactamase (ESBL) Gram-negative activity against multidrug-resistant organisms (including MRSA) associated with these indications, making it an attractive treatment option. *In vitro* and clinical studies suggest that ceftaroline has a low propensity for resistance

development by key pathogens associated with cSSTI and CAP. Ceftaroline has low drug-drug interaction potential. Ceftaroline has an acceptable safety and tolerability profile, which is consistent with that of approved cephalosporin antibiotics.

In conclusion, both the Delegate and the clinical evaluator accept that efficacy has been demonstrated with Zinforo in the treatment of patients with cSSTI and CAP. The primary efficacy outcome, clinical cure rate at TOC, is a well recognised, widely used endpoint to establish the ultimate clinical outcome for antibiotic therapy, that is, cure of the infection. Furthermore, efficacy has been demonstrated compared to antibiotic therapy which both deem to be acceptable standard of care in Australia for the two infection types. The observed high clinical cure and microbiological success rates combined with safety and the use of Zinforo in the treatment of adult patients with cSSTI and CAP. Consequently, approval should be proposed in accordance with the positive Delegate and clinical evaluator recommendations.

Bacterial resistance

As noted by the ACSOM, there is an increasing prevalence of formal antimicrobial stewardship (AMS) programs within Australian healthcare institutions. AMS programs aim to optimise antibiotic use through reduction of inappropriate use, improved patient outcomes and reduced adverse consequences of antibiotic use (including resistance). In addition to the recommendations within the relevant local treatment guidelines, this approach also takes into account the local microbiology and antibiotic susceptibility patterns current at that point in time.

The majority of Australian hospitals are now implementing AMS programmes. AstraZeneca was already planning to engage with the AMS committees in each hospital regarding our antibiotic range (including ceftaroline) to ensure that antibiotics in Australia are made available to appropriate patients and, in the words of the ACSOM “to avoid squandering the benefits of [new antibiotics] by overuse”.

With respect to local antibiotic susceptibility patterns, the proposed Zinforo PI already includes Australian surveillance data from the 2010 (SENTRY) program. In addition, AstraZeneca has established a global surveillance program to monitor and track the susceptibility of key pathogens to ceftaroline fosamil in various global geographic regions including Australia. Ongoing annual surveillance will permit a longitudinal analysis of any emerging phenotypes. This, combined with review of susceptibility data from scientific literature, will allow assessment of any potential emerging bacterial resistance concerns.

The sponsor subsequently provided further details on this program (including a copy of the final protocol, reporting periods and number of Australian sites) to the OPR as a separate response to the RMP evaluation recommendations.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit – risk profile for the modified indication;

For the treatment of patients with the following infections, proven or strongly suspected to be caused by designated susceptible bacteria:

- *Complicated skin and soft tissue infections*
- *Community-acquired pneumonia*

In making this recommendation, the ACPM noted the strong safety signal for the potential for haemolytic anaemia and agreed with the delegate that the inclusions in the PI and CMI

and the proposed conditions of registration are appropriate to inform prescribers and consumers on these risks.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically recommended:

- Strengthening the statement in the *Precautions / Adverse Reactions* section of the PI, to emphasise the higher incidence of positive direct Coombs' test and the potential risk of haemolytic anaemia.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically agreed with the inclusion of the following:

- The implementation of the GPRMP with Addendum 1 – Australian Risk Minimization Activities, RMP and subsequent revisions as agreed with the OPR.

The ACPM advised that the 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 Zinforo ceftaroline fosamil 600mg powder for injection vials, indicated for:

Zinforo is indicated for the treatment of patients with the following infections proven or strongly suspected to be caused by designated susceptible bacteria:

- *Complicated skin and soft tissue infections*
- *Community-acquired pneumonia*

Specific conditions applying to these therapeutic goods

The implementation in Australia of ceftaroline GPRMP version 2 dated 18 November 2011, including Australian Specific Annex (ASA) Version 2 dated 14 December 2012 included with submission PM-2011-03149-3-2, and any subsequent revisions, as agreed with the TGA and its OPR (Refer OPR Report 17 January 2013 –not included in this AusPAR).

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<http://www.tga.gov.au>