AUSTRALIAN PRODUCT INFORMATION – ZINFORO® (CEFTAROLINE FOSAMIL)

1. NAME OF THE MEDICINE

Ceftaroline fosamil monoacetate monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 600 mg of the prodrug, ceftaroline fosamil (equivalent to 530 mg active ceftaroline).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

Zinforo is a sterile, pyrogen-free pale yellowish-white to light yellow powder.

The reconstituted diluted solution is a pale yellow solution that is free of any particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 (cSSTI).
- Community-acquired pneumonia (CAP).

4.2 Dose and method of administration

Dosage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zinforo and other antibiotics, Zinforo should be used to treat only cSSTI or CAP that are proven or strongly suspected to be caused by designated susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibiotic therapy. In the absence of such data, local epidemiology and susceptibility patterns using local Antimicrobial Stewardship (AMS) recommendations and Therapeutic Guidelines must be used.

The recommended dosage of Zinforo, the frequency of dosing and infusion times are summarised in Table 1 below. The duration of treatment should be guided by the type of infection to be treated, its severity, and the patient's clinical response.

Table 1: Dosage in patients with creatinine clearance (CrCL) > 50 mL/min*

Infection/Duration of treatment	Age group	Dosage	Infusion time/Frequency
Standard Dose			
cSSTI[a]/Duration of treatment is 5 – 14 days	Adults and adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	600 mg	5 – 60 min every 12 hours[b]
	Adolescents aged from 12 years to < 18 years bodyweight < 33 kg **and** children ≥ 2 years to < 12 years	12 mg/kg to a maximum of 400 mg	5 – 60 mins every 8 hours[b]
	≥ 2 months to < 2 years	8 mg/kg	
	Birth to < 2 months	6 mg/kg	60 mins every 8 hours[b]
CAP/Duration of treatment is 5 – 7 days	Adults and adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	600 mg	5 – 60 min every 12 hours[b]
	Adolescents aged from 12 years to < 18 years bodyweight < 33 kg **and** children ≥ 2 years to < 12 years	12 mg/kg to a maximum of 400 mg	5 – 60 mins every 8 hours[b]
	≥ 2 months to < 2 years	8 mg/kg	
	Birth to < 2 months	6 mg/kg	60 mins every 8 hours[b]
High Dose			
cSSTI confirmed or suspected to be caused by *S. aureus* with MIC = 2 mg/L or 4 mg/L[a, c] to ceftaroline. Duration of treatment is 5 – 14 days.	Adults	600 mg	120 mins every 8 hours.
	Adolescents and children aged from ≥ 2 years to < 18 years	12 mg/kg to a maximum of 600 mg	
	≥ 2 months to < 2 years	10 mg/kg	

* Calculated using the Cockcroft-Gault formula for adults and Schwartz formula (in mL/min/1.73 m^2) for paediatric patients.

[a]: For treatment of *S. aureus* for which the ceftaroline MIC is ≤ 1 mg/L, the standard dose is recommended.

[b]: The 5 minute infusion time and neonatal recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties, Clinical trials.

[c]: High dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See Sections 4.4 Special warnings and precautions for use, cSSTI caused by *S. aureus* with an MIC > 1 mg/L to ceftaroline and 5.1 Pharmacodynamic properties, Clinical trials.

Method of administration

Intravenous (IV) infusion.

Standard aseptic techniques should be used for solution preparation and administration.

Zinforo powder should be reconstituted with 20 mL of sterile water for injections and the resulting reconstituted solution must then be immediately diluted prior to use. The resulting

reconstituted solution should be shaken prior to being transferred to an infusion bag or bottle containing one of the following diluents:

- sodium chloride 9 mg/mL (0.9%) solution for injection
- dextrose 50 mg/mL (5%) solution for injection
- sodium chloride 4.5 mg/mL and dextrose 25 mg/mL (0.45% sodium chloride and 2.5% dextrose) solution for injection
- Lactated Ringer's solution.

It must not be mixed with any other medications.

A 250 mL, 100 mL or 50 mL infusion bag can be used to prepare the infusion.

The total time interval between starting reconstitution and completing preparation of the IV infusion should not exceed 30 minutes.

One mL of the reconstituted solution contains 30 mg of ceftaroline fosamil.

Infusion volumes for children/adolescents will vary according to the weight of the child/adolescent. The infusion solution concentration during preparation and administration should not exceed 12 mg/mL ceftaroline fosamil.

Each Zinforo vial is for single use in one patient only.

Stability after reconstitution and dilution

After reconstitution

The reconstituted vial must be diluted immediately prior to use.

After dilution

To reduce microbial hazard, the Zinforo IV infusion solution should be administered as soon as practicable after preparation. If storage is necessary, hold at 2 to 8°C (Refrigerate. Do not freeze) for not more than 24 hours or not more than 6 hours at room temperature (including infusion time). The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 to 8°C and up to 6 hours at room temperature.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Dosage adjustment

Renal impairment

The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 mL/min (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties, Renal impairment), as shown in Table 2. The recommended durations of treatment are the same as those shown in Table 1.

Dose recommendations for children and adolescents are based on PK modelling.

For end stage renal disease (ESRD), there is insufficient information to recommend dosage adjustments in adolescents aged from 12 to < 18 years with bodyweight < 33 kg and in children aged from 24 months to 12 years. There is insufficient information to recommend dosage adjustments in children aged from 2 to < 24 months with moderate or severe renal impairment or ESRD.

Table 2: Dosage in patients with renal impairment (CrCL ≤ 50 mL/min)

Infection/ Duration of treatment	**Age group**	**Creatinine clearance (mL/min)[a]**	**Dose**	**Infusion time/Frequency**
Standard dose				
cSSTI/Duration of treatment is 5 to 14 days. CAP/Duration of treatment is 5 to 7 days.	Adults and adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	> 30 to ≤ 50	400 mg	5 - 60 mins, every 12 hours[c]
		≥ 15 to ≤ 30	300 mg	
		ESRD including haemodialysis[b]	200 mg	
	Adolescents aged 12 to < 18 years with bodyweight < 33 kg) and children ≥ 2 years to < 12 years)	> 30 to ≤ 50	8 mg/kg to a maximum of 300 mg	5 – 60 mins, every 8 hours[c]
		≥ 15 to ≤ 30	6 mg/kg to a maximum of 200 mg	
High Dose				
cSSTI confirmed or suspected to be caused by *S. aureus* with MIC = 2 or 4 mg/L to ceftaroline. Duration of treatment is 5 – 14 days[d]	Adults	> 30 to ≤ 50	400 mg	120 mins every 8 hours
		≥ 15 to ≤ 30	300 mg	
		ESRD including haemodialysis[b]	200 mg	
	Adolescents and children from aged ≥ 2 years to < 18 years	> 30 to ≤ 50	10 mg/kg to a maximum of 400 mg	
		≥ 15 to ≤ 30	8 mg/kg to a maximum of 300 mg	

[a]: Calculated using the Cockcroft-Gault formula and Schwartz formula for paediatric patients (in mL/min/1.73 m^2). Dose is based on CrCL. CrCL should be closely monitored and the dose adjusted according to changing renal function.

[b]: Ceftaroline is haemodialysable, thus Zinforo should be administered after haemodialysis on haemodialysis days.

[c]: The 5 minute infusion time and neonatal recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties, Clinical trials.

[d]: The high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See Sections 4.4 Special warnings and precautions for use, cSSTI caused by *S. aureus* with an MIC > 1 mg/L to ceftaroline and 5.1 Pharmacodynamic properties, Clinical trials.

Hepatic impairment

No dosage adjustment is considered necessary in patients with hepatic impairment (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties, Hepatic impairment).

Elderly (> 65 years old)

No dosage adjustment is required for the elderly with CrCL values above 50 mL/min (see Section 5.2 Pharmacokinetic properties, Elderly (> 65 years old)).

Paediatric patients < 2 months of age

There are limited clinical data in patients less than 2 months of age. Therefore, the recommended dosage of Zinforo shown in Table 1 for paediatric patients < 2 months of age is based on pharmacokinetic-pharmacodynamic modelling and simulation (see Section 4.2 Dose and method of administration).

4.3 Contraindications

Hypersensitivity to ceftaroline fosamil or L-arginine (excipient).

Hypersensitivity to the cephalosporin class of antibiotics.

Immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of β-lactam antibiotic (e.g., penicillins or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all β-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions are possible (see Sections 4.3 Contraindications and 4.8 Adverse effects (undesirable effects)).

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other β-lactam antibiotics may also be hypersensitive to ceftaroline fosamil. Before initiating therapy with Zinforo, careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. If a patient developed an immediate and severe hypersensitivity (e.g., anaphylactic reaction) previously to any type of β-lactam antibiotic, ceftaroline fosamil should not be administered (see Section 4.3 Contraindications).

If a severe allergic reaction occurs, Zinforo should be discontinued and appropriate measures taken.

***Clostridioides difficile*-associated diarrhoea**

Antibacterial-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including Zinforo and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of Zinforo (see Section 4.8 Adverse effects (undesirable effects)). In such circumstance, the discontinuation of therapy with Zinforo and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Patients with pre-existing seizure disorder

Clinical study experience with ceftaroline in patients with pre-existing seizure disorders is limited. Therefore, Zinforo should be used with caution in this patient population. As with

other cephalosporins, seizures have occurred in ceftaroline toxicology studies at 7-25 times human C_{max} levels.

Coombs test (direct antiglobulin test) seroconversion and potential risk of haemolytic anaemia

The development of a positive Coombs test (direct antiglobulin test) may occur during treatment with cephalosporins. The incidence of Coombs test seroconversion in patients receiving ceftaroline fosamil was 11.2% in the five pooled pivotal Phase 3 studies with administration every 12 hours (600 mg administered over 60 minutes every 12 hours) and 32.3% in a study in patients receiving ceftaroline fosamil every 8 hours (600 mg administered over 120 minutes every 8 hours). See Section 4.8 Adverse effects (undesirable effects). In clinical studies there was no evidence of haemolysis in patients who developed a positive Coombs test on treatment. However, the possibility that haemolytic anaemia may occur in association with cephalosporins including Zinforo treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zinforo should be investigated for this possibility.

Limitations of clinical data

cSSTI caused by S. aureus with an MIC > 1 mg/L to ceftaroline

There are limited clinical trial data on the use of ceftaroline to treat cSSTI caused by *S.aureus* with an MIC of > 1 mg/L. The recommended dosages of Zinforo shown in Tables 1 and 2 for the treatment of cSSTI caused by *S. aureus* with ceftaroline MIC of 2 or 4 mg/L are based on pharmacokinetic-pharmacodynamic modelling and simulation (see Sections 4.2 Dose and method of administration and 5.1 Pharmacological properties, Clinical trials, Complicated skin and soft tissue infections with systemic inflammatory response or underlying comorbidities (COVERS)). Zinforo should not be used to treat cSSTI due to *S. aureus* for which the ceftaroline MIC is > 4 mg/L.

Infusion times of less than 60 minutes

Infusion times of less than 60 minutes are based on pharmacokinetic and pharmacodynamic analyses only.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics (including ceftaroline fosamil). When SCAR is suspected, ceftaroline should be discontinued immediately and an alternative treatment should be considered.

Appropriate use of antibiotics

Consideration should be given to official guidance on the appropriate choice and dose of antibiotics using AMS and Therapeutic Guidelines. (see also Sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties, Susceptibility testing).

Non-susceptible organisms

Superinfections may occur as with other antibiotics.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Use in renal impairment

Dosage adjustments are required in adults, adolescents and children with creatinine clearance (CrCL) ≤ 50 mL/min (see Section 4.2 Dose and method of administration, Renal impairment).

There is insufficient information to recommend dosage adjustments in adolescents with ESRD aged from 12 to < 18 years and with bodyweight < 33 kg and in children with ESRD aged from 24 months to < 12 years. There is insufficient information to recommend dosage adjustments in children aged < 24 months with moderate or severe renal impairment or ESRD.

Relative overdosing could occur in patients with moderate to severe renal impairment. Neurological sequelae, including encephalopathy, have been noted in cases where beta-lactam antibiotics (including cephalosporins) have been given to patients with impaired renal function without reducing the dose (see Section 4.9 Overdose).

Use in the elderly

No dose adjustment is required in the elderly with CrCL values > 50 mL/min (see Sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Paediatric use

Dose adjustments are required for neonates, infants, children and for adolescents aged 12 to < 18 years with bodyweight < 33 kg (see Section 4.2 Dose and method of administration).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No clinical drug-drug interaction studies have been conducted with ceftaroline.

The interaction potential of ceftaroline on drugs metabolised by P450 enzymes is expected to be low, since ceftaroline is not an inhibitor (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) nor an inducer (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5) of P450 enzymes *in vitro*. Ceftaroline is not metabolised by P450 enzymes *in vitro*, so co-administered P450 inducers or inhibitors are unlikely to influence the pharmacokinetics of ceftaroline.

In vitro, ceftaroline is not transported by efflux transporters P-gp and BCRP. Ceftaroline does not inhibit P-gp, therefore an interaction with substrates, such as digoxin, is not expected. Ceftaroline is a weak inhibitor of BCRP, but the effect is too small to be clinically relevant. *In vitro* studies demonstrated that ceftaroline is not a substrate of, nor did it inhibit the renal uptake transporters OCT2, OAT1 and OAT3*;* drug-drug interactions with drugs that inhibit active

renal secretion (e.g., probenecid) or with drugs that are substrates of these transporters would therefore not be expected.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No adverse effects were observed on fertility of male and female rats given up to 450 mg/kg/day (approximately 4-fold higher than the maximum recommended human dose based on body surface area).

Use in pregnancy – Pregnancy Category B1

No clinical data on pregnancies are available for ceftaroline. Zinforo should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.

Animal studies with ceftaroline fosamil do not indicate harmful effects with respect to pregnancy, parturition or postnatal development. Reproductive studies in pregnant rabbits resulted in an increased foetal incidence of angulated hyoid alae, a common skeletal variation in rabbit foetuses, at systemic exposures around 0.6 times those produced in humans dosed at 600 mg twice daily. In the rat, no adverse effects were observed on embryofoetal or postnatal development at systemic exposures around 2-4 times those produced in humans dosed at 600 mg twice daily.

Use in lactation

It is not known whether ceftaroline is excreted in human milk. As many β-lactams are excreted in breast milk, women who are breast-feeding should be treated with Zinforo only if clearly indicated and interruption of breast feeding is recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Undesirable effects may occur which may have an effect on ability to drive and use machines (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

Clinical trial experience

Adults

The four Phase 3 clinical trials (two in cSSTI and two in CAP) included 1305 adult patients treated with Zinforo (600 mg administered over 60 minutes every 12 hours).

The safety profile of Zinforo is consistent with that expected of a cephalosporin antibiotic. The incidences of treatment-emergent adverse events in the initial pooled Phase 3 cSSTI and CAP trials were similar in Zinforo and comparator groups (45.7% versus 46.7%, respectively). The most common adverse reactions occurring in ≥ 3% of patients treated with Zinforo in these initial trials were diarrhoea, headache, nausea, rash and pruritus, and were generally mild or moderate in severity.

The treatment-emergent adverse events that occurred in at least 1% of patients in the Phase 3 cSSTI and initial CAP active comparator trials are listed in Table 3 regardless of causality.

Table 3: Treatment emergent adverse events occurring in ≥ 1% of patients in the Phase 3 cSSTI and CAP studies**

Preferred term	Percentage of patients (%)			
	cSSTI		CAP	
	Zinforo (N=692)	V + A (N=686)	Zinforo (N=613)	Ceftriaxone (N=615)
Diarrhoea*	4.9	3.8	4.2	2.6
Headache*	5.2	4.5	3.4	1.5
Nausea*	5.9	5.1	2.3	2.3
Insomnia	2.5	2.5	3.1	2.3
Constipation	2.6	2.6	1.5	1.0
Vomiting*	2.9	2.6	1.1	0.3
Pruritus*	3.5	8.2	0.2	0.5
Hypokalaemia	1.4	2.2	2.3	2.4
Rash*	3.2	2.5	0.3	0.3
Hypertension	1.3	1.5	2.3	2.6
Phlebitis*	0.4	0.7	2.8	2.1
Dizziness*	2.0	1.2	0.5	0.3
Pruritis generalised*	2.2	2.8	0	0
Abdominal pain*	1.3	1.0	0.8	0.5
Blood pressure increased	1.3	1.3	0.8	0.7
Alanine aminotransferase increased*	1.2	1.7	0.8	1.0
Pyrexia*	1.3	2.3	0.7	0.8

V+A – Vancomycin + aztreonam; N – total number of patients

* Adverse drug reaction associated with Zinforo.

** 1% cut-off based on the frequency of events in the pooled Zinforo cSSTI/CAP groups.

Infusion site reactions (erythema, phlebitis and pain) were commonly reported with use of Zinforo and comparator groups.

In addition, a study in Asia of 381 adult patients with CAP treated with Zinforo (600 mg administered over 60 minutes every 12 hours) demonstrated that the safety profile of Zinforo in these patients was similar to that observed in the pooled Phase 3 cSSTI and initial CAP studies. In addition, dyspepsia, asthenia, abnormal hepatic function, urinary tract infection and decreased appetite were commonly reported in the Zinforo group.

A study (COVERS) was conducted of 506 adult patients with cSSTI treated with Zinforo (600 mg administered over 120 minutes every 8 hours). The most common adverse reactions occurring in ≥ 3% of patients treated with Zinforo were nausea, headache, and rash. The safety profile of Zinforo was similar to that observed in previous pooled Phase 3 studies with the exception of both a greater incidence of rash in Asian patients and a greater incidence of DAGT seroconversion (see Section 4.4 Special warnings and precautions for use).

Rash was observed at a common frequency in the pooled Phase 3 studies in cSSTI with administration of Zinforo every 12 hours (600 mg administered over 60 minutes every 12 hours) and the COVERS study in cSSTI with administration every 8 hours (600 mg

administered over 120 minutes every 8 hours). However, the frequency of rash in the subgroup of Asian patients receiving Zinforo every 8 hours (COVERS) was very common (18.5%).

Adverse reactions

The following adverse drug reactions have been observed with Zinforo during the Phase 3 clinical trials (including the Phase 3 CAP study in Asia).

Table 4: Adverse drug reactions that occurred with Zinforo in Phase 3 cSSTI and CAP studies

Frequency	System organ class	Event
Very common (≥ 1/10)	Investigations	Coombs Direct Test Positive[a]
Common (< 1/10 to ≥ 1%)	Hepatobiliary disorders	Increased transaminases
	Skin and subcutaneous tissue disorders	Rash, pruritus
Uncommon (≥ 0.1 to < 1%)	Blood & lymphatic system disorders	Anaemia; leucopenia; thrombocytopenia; neutropenia
	Immune system disorders	Hypersensitivity/anaphylaxis[b]
	Skin & subcutaneous disorders	Urticaria
	Infections and infestations	*Clostridioides difficile* colitis[a]
	Investigations	Prothrombin time prolonged; international normalised ratio increased
	Renal & urinary disorders	Blood creatinine increased
Rare (≥ 0.01 to < 0.1%)	Blood & lymphatic system disorders	Agranulocytosis

[a]: See Section 4.4 Special warnings and precautions for use.
[b]: See Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use.

Kounis syndrome

Acute coronary syndrome associated with an allergic reaction (Kounis syndrome) has been reported with other beta-lactam antibiotics.

Children and adolescents

The safety assessment in children and adolescents is based on the safety data from 2 clinical trials in which 227 patients aged from 2 months to 17 years with cSSTI or CAP received ceftaroline in which the safety profile was similar to that observed in the adult population. In addition, 30 patients received ceftaroline in a complicated CAP study and 62 patients received a single dose of ceftaroline in PK studies and no additional safety concerns were identified from these supportive studies.

In addition, the safety assessment in neonates (age range from birth to less than 2 months) is based on the safety data from 2 trials in which 11 patients with late-onset sepsis received ceftaroline fosamil at 4 or 6 mg/kg as a 60 minute infusion every 8 hours (q8h) and 23 patients with a suspected or confirmed bacterial infection received only a single dose of ceftaroline fosamil at 8 mg/kg as a 60 minute infusion. Overall, the adverse events reported in these studies were consistent with the known safety profile for Zinforo.

Post-marketing experience

Blood and lymphatic system disorders: Eosinophilia.

Skin and other subcutaneous tissue disorders: Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). Also see Section 4.4 Special warnings and precautions for use, Severe cutaneous adverse reactions.

Nervous system disorders: Encephalopathy, seizures, myoclonus.

Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms

Intentional overdosing of ceftaroline fosamil is unlikely, although relative overdosing can occur particularly in patients with moderate to severe renal impairment. Limited data in patients receiving higher than recommended Zinforo dosages show similar adverse reactions as observed in the patients receiving recommended dosages. Treatment under such circumstances should follow local standard medical practice.

Recommended treatment

Ceftaroline can be removed by haemodialysis over a 4-hour dialysis session. Approximately 74% of a given dose was recovered in the dialysate.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ceftaroline fosamil is a semi-synthetic prodrug from the cephalosporin class of β-lactam antibiotics.

Ceftaroline is a cephalosporin with activity against Gram-positive and Gram-negative bacteria. *In vitro* studies have shown that ceftaroline is bactericidal due to inhibition of bacterial cell wall synthesis by binding to penicillin binding proteins (PBPs). Ceftaroline is also active against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin non-susceptible

Streptococcus pneumoniae (PNSP) due to its affinity for the altered PBPs found in these organisms.

Pharmacokinetic/pharmacodynamic relationship

As with other β-lactam antibiotics, the percent time above the minimum inhibitory concentration (MIC) of the infecting organism over the dosing interval (%T > MIC) has been shown to best correlate with the antimicrobial activity of ceftaroline.

Mechanisms of resistance

Ceftaroline is not active against strains of *Enterobacterales* 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.

Cross-resistance

Unlike other cephalosporins, ceftaroline is active against most MRSA and PNSP due to its ability to bind to the altered PBPs in these organisms that commonly confer insusceptibility to other β-lactam agents.

Interaction with other antibiotics

In vitro studies have not demonstrated any antagonism between ceftaroline in combination with other commonly used antibiotics (e.g., amikacin, azithromycin, aztreonam, daptomycin, levofloxacin, linezolid, meropenem, tigecycline and vancomycin).

Susceptibility testing

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information on resistance is important. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is questionable.

The susceptibility to ceftaroline of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

As detailed in Section 5.1 Pharmacodynamic properties, Clinical trials below, efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to ceftaroline *in vitro*.

Complicated skin and soft tissue infection (cSSTI):

Also refer Table 7.

Gram-positive aerobes

S. aureus (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius* and *S. constellatus*) and *Streptococcus dysgalactiae*.

Gram-negative aerobes

Escherichia coli, *Klebsiella pneumoniae*, *Klebsiella oxytocoa*, *Morganella morganii.*

Community acquired pneumonia (CAP):

Also refer Table 11 and Table 13.

Gram-positive aerobes

S. pneumoniae (including cases with concurrent bacteraemia) and *S. aureus* (methicillin-susceptible strains only as MRSA was an exclusion criterion). See Section 5.1 Pharmacodynamic properties, Clinical trials for details.

Gram-negative aerobes

E. coli, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae.*

***In vitro* susceptibility**

Clinical efficacy has not been established against the following relevant pathogens, although *in vitro* studies suggest that they would be susceptible to ceftaroline in the absence of acquired mechanisms of resistance.

Gram-positive anaerobes

Peptostreptococcus spp.

Gram-negative anaerobes

Fusobacterium spp.

In vitro data indicate that the following species are not susceptible to ceftaroline: *Chlamydophila* spp., *Legionella* spp., *Mycoplasma* spp. and *Pseudomonas aeruginosa*.

Australian antibiotic resistance prevalence data

A surveillance study was conducted to examine the susceptibility of ceftaroline tested against contemporary clinical isolates collected from Australia in 2010. A total of 1523 isolates were collected from 6 sites in 6 different states/territories across the country. Sources of isolates were specimens obtained from patients with infections of the blood stream (22.9%), skin/soft tissue (33.0%), respiratory tract (38.4%), urinary tract (3.4%) or other (2.4%) infection types. Where applicable, susceptibility interpretive criteria applied were *Clinical Laboratory Standards Institute* (CLSI) M100-S21 (2011). Data are summarised in Table 5 below.

A surveillance study was conducted to examine the susceptibility of ceftaroline tested against contemporary clinical isolates collected from Australia in 2015. A total of 766 isolates (including paediatric isolates: 21 from ≤ 1 year old and 74 from 2-17 years old) were collected from 5 sites in 4 different states across the country.

Overall, the 2015 surveillance study showed similar susceptibility results as in 2010. There were no significant changes in the MIC range (mg/L) and the MIC_{90} results did not vary by more than 2-3 fold dilution for each genus/species evaluated. With respect to total *S. aureus* tested, there was a notable increase in the incidence of MRSA isolated in 2015 (62% or 149/237) vs (28% or 131/466)) isolated in 2010, however, the MIC_{90} of 1 mg/L for MRSA remained the same in both study years. The Streptococci species (including the Pneumococcal isolates) and the Gram-negative fastidious pathogens (*H. influenzae* and *M. catarrhalis*) remained highly susceptible to ceftaroline. For *Enterobacterale*, the non-ESBL phenotypes of *E. coli*, *Klebsiella* species, and *P. mirabilis* had reported MIC_{90s} of ≤ 0.5 mg/L that were within

the CLSI and EUCAST susceptible breakpoints. In 2015, ceftaroline showed variable activity against *M. morganii* with an MIC range of 0.12 to > 32 mg/L that was comparable to 2010. During this 5-year surveillance period, ceftaroline tested with expected potency against the prescribed pathogens isolated in Australia.

The surveillance study conducted in 2016 to examine the susceptibility of ceftaroline against contemporary clinical isolates were collected from 5 sites in 4 different states across Australia. A total of 1145 isolates (including paediatric isolates: 44 from ≤ 1 year old and 85 from 2-17 years old) were collected. No major differences were found in ceftaroline activity between LRTI, SSTI and blood subsets as well as from subsets from paediatric and adult patients and the population as a whole except for *K. oxytocoa* where ceftaroline activity against SSTI isolates were greater against the general population (MIC_{90} > 128 mg/L), *M. morganii* where ceftaroline activity against SSTI isolates was greater than against the general population (MIC_{90} of 128 mg/mL) and *P. mirabilis* where ceftaroline activity against LRTI isolates was greater than against the entire collection (MIC_{90} 16 mg/L versus > 128 mg/L). Longitudinal analysis of data from 2012 through 2016 showed no notable decreasing trends in ceftaroline susceptibility of any species at CLSI, EUCAST or PK/PD breakpoints.

Longitudinal analysis of ceftaroline *in vitro* activity in Australia from 2012 to 2019 is presented in the table below. The *in-vitro* data in the table below were conducted on a total of 12,196 isolates collected between 2004 to 2019 from 16 investigative sites across the country. Ceftaroline had good activity against *S. aureus* clinical isolates, with an overall MIC_{90} value of 1 mg/L and 90.6% of isolates susceptible to ceftaroline. The activity of ceftaroline was greater against the MSSA than the MRSA isolates with MIC_{90} values 0.25 and 1 mg/L, respectively. Potent activity was observed against *S. pneumoniae*, with a ceftaroline MIC_{90} of 0.12 mg/L. Reduced penicillin susceptibility had an impact on the ceftaroline MIC distribution as the compound displayed MIC_{90} values of 0.015, 0.12, and 0.25 mg/L against penicillin-susceptible, -intermediate and –resistant strains, respectively.

Table 5: *In vitro* activity from 2010 and 2012-2019 Australian bacterial surveillance

Isolates	**Minimum inhibitory concentration (MIC) [µg/mL]**					
	2010			**2012-2019**		
	n[a]	**MIC_{90}**	**Range**	**n[a]**	**MIC_{90}**	**Range**
Total	**1523**	**-**	**-**	**12,196^**	**-**	**-**
Gram-positive aerobes						
S. aureus	466	0.5	0.06-2	2164	1	≤ 0.06 – 2
MSSA	335	0.25	0.06-0.5	935	0.25	≤ 0.06 – 0.5
MRSA	131	1	0.25-2	1229	1	0.12 – 2
Coagulase negative Staphylococci	8	-	≤0.008 - 0.5	297	1	≤ 0.015 – 2
MSCoNS	2	-	≤ 0.008 - 0.12	78	0.12	≤ 0.015 – 0.5
MRCoNS	6	-	0.25 - 0.5	219	2	0.06 – 2
E. faecalis	43	8	0.5 - 16	-	-	-
β-haemolytic Streptococci	118	0.015	≤ 0.008 - 0.03	-	-	-
Group A Streptococcus	61	≤ 0.008	≤ 0.008	-	-	-
Group B Streptococcus	25	0.03	≤ 0.008 - 0.03	-	-	-
Viridans group Streptococci	33	0.06	≤ 0.008 - 0.25	-	-	-
S. pneumoniae	170	0.06	≤ 0.008 - 0.25	709	0.12	≤ 0.004 – 0.5

Isolates	Minimum inhibitory concentration (MIC) [µg/mL]					
	2010			2012-2019		
	n[a]	MIC_{90}	Range	n[a]	MIC_{90}	Range
PSSP	121	≤ 0.008	≤ 0.008 - 0.015	469	0.015	≤ 0.004 – 0.03
PISP	34	0.06	≤ 0.008 - 0.12	154	0.12	0.008 – 0.25
PRS	15	0.25	0.06 - 0.25	86	0.25	0.06 – 0.5
Gram-negative aerobes						
Citrobacter spp	40	32	0.06 - > 32	255	64	≤ 0.03 – > 128
Enterobacterales	265	2	0.015 - > 16	3096	16	≤ 0.015 – > 128
Enterobacter spp.	66	> 32	0.06 - > 32	268	64	≤ 0.03 – > 128
E. coli	128	2	0.015 - > 32	941	32	≤ 0.015 – > 128
ESBL phenotype	9	-	32 - > 32	-		
non-ESBL phenotype	119	0.5	0.015- > 32	-		
H. influenzae	152	0.03	≤ 0.008 - 0.06	214	0.03	≤ 0.015 – > 1
β-lactamase positive	39	0.06	≤ 0.008 - 0.06	50	0.03	≤ 0.015 – > 1
β-lactamase negative	113	0.015	≤ 0.008 - 0.06	164	0.03	≤ 0.015 – 0.12
H. parainfluenzae	9	-	≤ 0.008 - 0.015	12	0.12	≤ 0.015 – 1
K. pneumoniae	52	0.5	0.03 - > 32	788	1	0.015 – > 128
ESBL phenotype	4	-	4 - > 32	-		
non-ESBL phenotype	48	0.5	0.03 - 1	-		
K. oxytocoa	10	> 32	0.06 - > 32	190	> 8	0.03 - > 128
ESBL phenotype	2	-	> 32	-		
non-ESBL phenotype	8	-	0.06 - 0.5	-		
Moraxella catarrhalis	36	0.12	≤ 0.008 - 0.5	83	0.25	≤ 0.015 – 2
Morganella morganii	2	> 32	0.06 - > 32	82	64	≤ 0.015 – > 128
**P. aeruginosa*	100	> 32	0.5 - > 32	-	-	-
Serratia marcescens	39	8	0.5 - > 32	80	4	0.06 – 32

MSSA – Methicillin-susceptible *S. aureus*; MRSA – Methicillin-resistant *S. aureus*; MSCoNS – Methicillin-susceptible coagulase negative Staphylococci; MRCoNS – Methicillin-resistant coagulase negative Staphylococci; spp – Species; ESBL – Extended-spectrum β-lactamase; *Not susceptible to ceftaroline; PSSP = penicillin-susceptible *S. pneumoniae* (penicillin < 0.06 mg/L); PISP = penicillin-intermediate *S. pneumoniae* (penicillin 0.12 – 1 mg/L); PRSP = penicillin-resistant S. pneumoniae (penicillin ≥ 2 mg/L).

[a]: Species with n < 10 are not represented individually but are included within the combined species. Phenotypes with n < 10 are listed but MIC90 are not calculated for n < 10.

^: Isolates collected between 2004 and 2019 from 16 investigative sites in Australia.

Clinical trials

Complicated skin and soft tissue infections (cSSTI)

The efficacy and safety of Zinforo in cSSTI was established in 2 identical randomised, multicentre, multinational, double-blind studies (CANVAS 1 and 2) comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to vancomycin plus aztreonam (1 g vancomycin administered intravenously over 60 minutes followed by 1 g aztreonam administered intravenously over 60 minutes every 12 hours). Treatment duration was 5 to 21 days.

A total of 1396 adults with documented cSSTI were enrolled. 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 infection in

patients with either pre-existing diabetes mellitus (DM) or peripheral vascular disease (PVD). Key exclusion criteria included third degree burns (or burns covering > 5% body surface area), diabetic foot ulcer or foot ulcer associated with PVD (and accompanied by osteomyelitis), immunosuppressed patients, patients with severe sepsis/septic shock, necrotizing fasciitis and peri-rectal abscess. Approximately 46% of patients had either pre-existing DM and/or PVD or presented with either bacteraemia or systemic inflammatory response syndrome (SIRS). The median age of patients was 48 years old; of which approximately 18% were 65 years or older. The median treatment duration was 7.0 (range: 1-22) and 8.0 (range: 1-21) days for Zinforo and vancomycin/aztreonam, respectively with the majority of patients receiving 5 to 10 days treatment.

The modified intent-to-treat (MITT) population included all patients who received any amount of study drug according to their randomised treatment group. The clinically evaluable (CE) population included patients in the MITT population with sufficient adherence to the protocol. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the CE and MITT patients.

Zinforo demonstrated high clinical cure and microbiological success rates (see Table 6) and was efficacious against cSSTI caused by MRSA and other common cSSTI pathogens (see Table 7). Clinical cure rates were similar across infection types and between patients with common co-morbidities (such as DM and PVD).

Table 6: Clinical cure and microbiological response rates at test of cure (TOC) for cSSTI studies (CE, MITT and/or ME populations)

	Zinforo n/N (%)	**V + A n/N (%)**	**Treatment difference (95% CI)**
CANVAS 1 clinical cure rate			
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)
CANVAS 2 clinical cure rate			
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)
Pooled data			
Clinical cure rate			
CE Overall	559/610 (91.6)	549/592 (92.7)	-1.1 (-4.2, 2.0)[a]
CE by selected co-morbidity, severity or infection sub-groups*			
PVD	80/90 (88.9)	75/84 (89.3)	-0.2 (-10, 9.7)[a]
DM	96/110 (87.3)	100/110 (90.9)	-3.5 (-12, 5.0)[a]
PVD & DM	19/25 (76.0)	20/27 (74.1)	N/A
SIRS or bacteraemia	135/152 (88.8)	146/156 (93.6)	-4.9 (-11.7, 1.5)[a]
Cellulitis	213/229 (93.0)	222/243 (91.4)	1.7 (-3.4, 6.7)[a]
Abscess	187/205 (91.2)	179/190 (94.2)	-3.0 (-8.4, 2.3)[a]
Infected wound	73/84 (86.9)	65/73 (89.0)	-2.2 (-12.8, 8.7)[a]
Infected ulcer	48/53 (90.6)	47/50 (94.0)	-3.5 (-15.7, 8.3)[a]
Infected burn	25/25 (100)	18/18 (100)	N/A
MITT	595/693 (85.9)	586/685 (85.5)	0.3 (-3.4, 4.0)[a]

	Zinforo n/N (%)	V + A n/N (%)	Treatment difference (95% CI)
Microbiological response rate (favourable) – ME	432/468 (92.3)	418/446 (93.7)	-1.4 (-4.8, 2.0)[a]

V+A – Vancomycin + aztreonam; CE – Clinically evaluable; MITT – Modified intention-to-treat; ME – Microbiologically evaluable; DM – Diabetes mellitus; PVD – Peripheral vascular disease; SIRS – Systemic inflammatory response syndrome (SIRS); CI – Confidence interval; N/A – Not applicable
[a]: Weighted difference
*Patients may be included in one or more of the following sub-groups.

Table 7: Clinical and microbiological success by baseline infecting pathogen from primary infection site or blood at TOC for pooled cSSTI studies (ME population)

	Clinical success		Microbiological success [a]	
Pathogen	**Zinforo n/N (%)**	**V + A n/N (%)**	**Zinforo n/N (%)**	**V + A n/N (%)**
Gram-positive	402/431 (93.3)	397/422 (94.1)	403/431 (93.5)	396/422 (93.8)
Staphylococcus aureus[b]	352/378 (93.1)	336/356 (94.4)	357/381 (93.7)	338/360 (93.9)
MSSA	212/228 (93.0)	225/238 (94.5)	214/228 (93.9)	225/238 (94.5)
MRSA	142/152 (93.4)	115/122 (94.3)	142/152 (93.4)	113/122 (92.6)
Streptococcus pyogenes	56/56 (100)	56/58 (96.6)	56/56 (100)	56/58 (96.6)
Streptococcus agalactiae	21/22 (95.5)	18/18 (100)	20/22 (90.9)	18/18 (100)
Streptococcus dysgalactiae	13/13 (100)	15/16 (93.8)	13/13 (100)	15/16 (93.8)
Streptococcus anginosus group[c]	12/13 (92.3)	15/16 (93.8)	12/13 (92.3)	15/16 (93.8)
Gram-negative	84/95 (88.4)	90/94 (95.7)	82/95 (86.3)	88/94 (93.6)
Escherichia coli	20/21 (95.2)	19/21 (90.5)	20/21 (95.2)	19/21 (90.5)
Klebsiella oxytocoa	10/12 (83.3)	6/6 (100.0)	11/12 (91.7)	5/6 (83.3)
Klebsiella pneumoniae	17/18 (94.4)	13/14 (92.9)	17/18 (94.4)	13/14 (92.9)
Morganella morganii	11/12 (91.7)	5/6 (83.3)	11/12 (91.7)	6/6 (100)

ME – Microbiologically evaluable; V+A – Vancomycin + aztreonam; MSSA – Methicillin-susceptible *S. aureus*; MRSA – Methicillin-resistant *S. aureus*
[a] Presumed eradication and/or eradication of causative pathogen; [b] Patients with both MRSA and MSSA counted twice; [c] Includes S. *anginosus, S. intermedius* and *S. constellatus*.

Complicated skin and soft tissue infections with systemic inflammatory response or underlying comorbidities (COVERS)

A total of 772 adults with cSSTI with evidence of systemic inflammation and/or underlying comorbidities were enrolled in a randomised, multicentre, double-blind study (COVERS) comparing ceftaroline fosamil (600 mg administered intravenously over 120 minutes every 8 hours) to vancomycin plus aztreonam. The MITT population included all patients who received any amount of study drug according to their randomised treatment group; patients had an average area of lesion size of 400 cm^2, approximately 40% of patients had SIRS, 86% had ≥ 2 severe local signs and/or symptoms or fever or elevated WBC, and > 60% had CRP > 50 mg/L, which was consistently higher than patients in the Phase 3 q12 hour cSSTI pool studies (CANVAS Studies). Treatment duration was 5 to 14 days. The CE population included patients in the MITT population with sufficient adherence to the protocol. The primary endpoint was clinical cure rate at the TOC visit in both the MITT and CE populations.

Table 8: Clinical cure rates at TOC in COVERS study after 5 to 14 days of therapy

	Ceftaroline n/N (%)	Vancomycin/Aztreonam n/N (%)	Treatment difference (2-sided 95% CI)
CE	342/395 (86.6)	180/211 (85.3)	1.3 (-4.3, 7.5)
MITT	396/506 (78.3)	202/255 (79.2)	-1.0 (-6.9, 5.4)

Table 9: Clinical cure rates by infecting pathogen from microbiologically evaluable patients with cSSTI (data from COVERS)

Organism	Ceftaroline N/N (%)	Vancomycin/Aztreonam n/N (%)
Gram-positive organisms		
Staphylococcus aureus	109/119 (91.6)	61/71 (85.9)
MSSA (methicillin- susceptible) strains)	88/94 (93.6)	49/57 (86.0)
MRSA (methicillin- resistant strains)	21/25 (84.0)	12/15 (80.0)
Streptococcus pyogenes	14/15 (93.3)	7/7 (100)
Streptococcus anginosus group[a]	16/18 (88.9)	4/4 (100)
Gram-negative organisms		
Escherichia coli	11/12 (91.7)	9/10 (90.0)
Klebsiella pneumoniae	5/7 (71.4)	3/4 (75.0)

[a]: Includes *S. anginosus*, *S. intermedius* and *S. constellatus*

Community-acquired pneumonia (CAP)

The efficacy and safety of Zinforo in CAP was established in 2 randomised, multicentre, multinational, double-blind, studies (FOCUS 1 and 2) comparing Zinforo [600 mg administered intravenously over 60 minutes every 12 hours] to ceftriaxone [1 g administered intravenously over 30 minutes every 24 hours]. The studies were identical except in one respect, in FOCUS 1 both treatment groups received 2 doses of oral clarithromycin (500 mg every 12 hours) as adjunctive therapy starting on Day 1. No adjunctive macrolide therapy was used in FOCUS 2. Treatment duration was 5 - 7 days.

A total of 1240 adults with new or progressive pulmonary infiltrate(s) on chest radiography with clinical signs and symptoms consistent with CAP of the Pneumonia Outcomes Research Team (PORT) risk class III or IV with the need for hospitalization (but not admitted to ICU) and IV therapy were enrolled in the studies. A key exclusion criterion included patients infected with pathogens known or suspected to be resistant to ceftaroline and ceftriaxone, such as atypical pathogens or *Pseudomonas* spp. In addition, patients with suspected or confirmed MRSA infections were excluded due to lack of activity of ceftriaxone against this pathogen. Other exclusion criteria included immunosuppressed patients, patients with severe sepsis/septic shock and patients with severe underlying lung disease. Approximately 38% of patients had a PORT score of IV and 30% had severe CAP as per the modified American Thoracic Society (ATS) criteria. The majority of patients (75%) had SIRS, with 36% with hypoxia, 19% with pleural effusion and 28% with multilobar infiltrates. The most common co-morbid conditions were structural lung disease (~25%), diabetes (~15%), cardiac impairment (~33%) and renal impairment (~50%; CrCL ≤ 80 mL/min). Approximately 48% of patients were 65 years or older. The median treatment duration was 7.0 days (range: 1-8) in both treatment arms, with the majority of patients receiving 5-7 days treatment.

The modified intent-to-treat efficacy (MITTE) population included all patients who received any amount of study drug according to their randomised treatment group and were in PORT risk class III or IV. The CE population included patients in the MITTE population with sufficient adherence to the protocol. The primary efficacy endpoint was the clinical response at the TOC visit in the co-primary populations of the CE and MITTE populations.

Zinforo demonstrated high clinical cure and microbiological success rates (see Table 10) and was efficacious against CAP caused by *S. pneumoniae* and other common CAP pathogens (see Table 11).

Table 10: Clinical cure and microbiological response rates at test of cure (TOC) for CAP studies (CE, MITTE and/or ME populations)

	Zinforo n/N (%)	**Ceftriaxone n/N (%)**	**Treatment difference (95% CI)**
FOCUS 1 clinical cure rate			
CE	194/224 (86.6)	183/234 (78.2)	8.4 (1.4, 15.4)
MITTE	244/291 (83.8)	233/300 (77.7)	6.2 (-0.2, 12.6)
FOCUS 2 clinical cure rate			
CE	193/235 (82.1)	166/215 (77.2)	4.9 (-2.5, 12.5)
MITTE	235/289 (81.3)	206/273 (75.5)	5.9 (-1.0, 12.7)
Pooled data			
Clinical cure rate			
CE Overall	387/459 (84.3)	349/449 (77.7)	6.7 (1.6, 11.8)[a]
CE by selected sub-groups*			
PORT III	249/287 (86.8)	217/274 (79.2)	7.5 (1.3, 13.8)[a]
PORT IV	138/172 (80.2)	132/175 (75.4)	4.7 (-4.1, 13.5)[a]
Presence of bacteraemia	15/21 (71.4)	10/17 (58.8)	12.6 (-17.6, 41.6)
No prior systemic antibacterial	235/274 (85.8)	191/255 (74.9)	11.2 (4.5, 18.0)[a]
Any prior systemic antibacterial	152/185 (82.2)	158/194 (81.4)	0.7 (-7.2, 8.6)[a]
MITTE	479/580 (82.6)	439/573 (76.6)	6.0 (1.4, 10.7)[a]
Microbiological response rate (favourable) – ME	134/154 (87.0)	119/147 (81.0)	6.1 (-2.3, 14.6)[a]

CAP – Community acquired pneumonia; CE – Clinically evaluable; MITTE – Modified intention-to-treat efficacy; ME – Microbiologically evaluable; CI – Confidence interval; PORT – Pneumonia Outcomes Research Team risk class

[a]: Weighted difference

*Patients may be included in one or more of the following sub-groups.

Table 11: Clinical and microbiological success by baseline infecting pathogen at TOC for pooled CAP studies (ME population)

Pathogen	**Clinical success**		**Microbiological success[a]**	
	Zinforo n/N (%)	**Ceftriaxone n/N (%)**	**Zinforo n/N (%)**	**Ceftriaxone n/N (%)**
Gram-positive				
Streptococcus pneumoniae	54/63 (85.7)	41/59 (69.5)	55/63 (87.3)	43/59 (72.9)
Staphylococcus aureus	18/25 (72.0)	15/27 (55.6)*	19/25 (76.0)	19/27 (70.4)*
MSSA	18/25 (72.0)	14/25 (56.0)	19/25 (76.0)	18/25 (72.0)

Pathogen	Clinical success		Microbiological success[a]	
	Zinforo n/N (%)	Ceftriaxone n/N (%)	Zinforo n/N (%)	Ceftriaxone n/N (%)
Gram-negative				
Haemophilus influenzae	15/18 (83.3)	17/20 (85.0)	15/18 (83.3)	17/20 (85.0)
Haemophilus parainfluenzae	16/16 (100.0)	15/17 (88.2)	16/16 (100)	16/17 (94.1)
Enterobacterales				
Escherichia coli	10/12 (83.3)	9/12 (75.0)	10/12 (83.3)	11/12 (91.7)
Klebsiella pneumoniae	13/13 (100.0)	10/12 (83.3)	13/13 (100)	10/12 (83.3)
Monomicrobial infections	95/111 (85.6)	80/102 (78.4)	98/111 (83.3)	84/102 (82.4)
Polymicrobial infections	36/43 (83.7)	31/45 (68.9)	36/43 (83.7)	35/45 (77.8)

CAP – Community acquired pneumonia; ME – Microbiologically evaluable; MSSA – Methicillin-susceptible *S. aureus*

[a]: Presumed eradication and/or eradication of causative pathogen.

*Includes 2 patients with methicillin-resistant *S. aureus*.

In addition, the efficacy and safety of Zinforo in Asian patients (including China, India, Korea, Taiwan and Vietnam) with CAP was established in a randomised, multicentre, double-blind study in comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to ceftriaxone (2 g administered intravenously over 30 minutes every 24 hours). The study design was similar to the initial Phase 3 CAP studies, with no adjunctive macrolide therapy as per FOCUS 2. Treatment duration was 5 to 7 days.

A total of 771 adults (385 and 386 in ceftaroline and ceftriaxone groups, respectively) with CAP as defined by radiographic and microbiologic inclusion criteria and whose severity of disease was a PORT Risk Class III or IV were randomised in the study. Patients also need to have acute illness of ≤ 7 days duration with at least 3 clinical signs or symptoms consistent with a lower respiratory tract infection. Key exclusion criterion were similar to the initial CAP studies including patients infected with pathogens known or suspected to be resistant to ceftaroline and ceftriaxone (e.g., *Pseudomonas* spp), and patients with suspected or confirmed MRSA infections (due to lack of activity of ceftriaxone against this pathogen).

Approximately 32% of patients had a PORT score of IV and ~60% of patients were 65 years or older. A high percentage of patients had a history of underlying lung disease: COPD (~28%), asthma (~6%), tuberculosis (~7%), chronic bronchitis (~4%), and bronchiectasis (~3%) and a low percentage (< 25%) of patients had received prior systemic antibacterial medication.

The primary objective was to determine the non-inferiority in the clinical cure rate of ceftaroline treatment compared with that of ceftriaxone treatment at the TOC visit in the CE population of adult hospitalised patients with CAP (lower boundary of the 95% confidence interval for the difference in response rate [ceftaroline – ceftriaxone] greater than -10%).

The non-inferiority of ceftaroline 600 mg versus ceftriaxone 2 g was demonstrated in both the CE and MITT populations (Table 12). Furthermore, based on the pre-defined criteria (lower boundary of the 95% confidence interval for the difference in response rate greater than 0%), the superiority of ceftaroline 600 mg versus ceftriaxone 2 g was demonstrated in adult patients with PORT risk class III or IV CAP in Asia.

Zinforo was efficacious against CAP caused by *S. pneumoniae* and other common CAP pathogens (see Table 13).

Table 12: Clinical cure and microbiological response rates at test of cure (TOC) for Asia CAP study (CE and MITT populations)

	Zinforo n/N (%)	**Ceftriaxone n/N (%)**	**Treatment difference (95% CI)**
Clinical cure rate			
CE	208/247 (84.2)	170/231(73.6)	10.6 (3.3, 18.0)
MITT	293/366 (80.1)	244/366(66.7)	13.4 (7.0, 19.7)
Microbiological response rate (favourable) - ME	48/55 (87.3)	45/59 (76.3)	11 (-3.5, 25.3)

CE – Clinically evaluable; MITT – Modified intention-to-treat; ME – Microbiologically evaluable; CI – Confidence interval

Table 13: Clinical and microbiological success by baseline infecting pathogen at TOC for Asia CAP study (ME population)

	Clinical success		**Microbiological success [a]**	
Pathogen	**Zinforo n/N (%)**	**Ceftriaxone n/N (%)**	**Zinforo n/N (%)**	**Ceftriaxone n/N (%)**
Gram-positive				
Streptococcus pneumoniae	19/22 (86.4)	13/15 (86.7)	19/22 (86.4)	13/15 (86.7)
*Staphylococcus aureus (*methicillin-susceptible strains only*)*	2/2 (100.0)	1/3 (33.3)	2/2 (100.0)	1/3 (33.3)
Gram-negative				
Haemophilus influenzae	9/10 (90.0)	6/7 (85.7)	9/10 (90.0)	6/7 (85.7)
Haemophilus parainfluenzae	0/0	4/6 (66.7)	0/0	4/6 (66.7)
Enterobacterales:				
Escherichia coli	3/3 (100.0)	5/6 (83.3)	3/3 (100.0)	5/6 (83.3)
Klebsiella pneumoniae	11/14 (78.6)	12/16 (75.0)	11/14 (78.6)	12/16 (75.0)

ME – Microbiologically evaluable; [a] Presumed eradication and/or eradication of causative pathogen

Children and adolescents

Complicated skin and soft tissue infections

The cSSTI paediatric trial was a randomised, parallel-group, active controlled trial in paediatric patients 2 months to < 18 years of age. A total of 163 children from 2 months to < 18 years of age with clinically documented cSSTI were enrolled in a randomised, multicentre, multinational, parallel group, active controlled trial comparing ceftaroline fosamil to vancomycin or cefazolin (each with optional aztreonam). Treatment duration was 5 to 14 days. A switch to oral therapy with either cephalexin, clindamycin, or linezolid after Study Day 3 was allowed. The Modified Intent-to-Treat (MITT) population included all patients who received any amount of study drug with a confirmed diagnosis of cSSTI. The primary objective was to evaluate the safety and tolerability of ceftaroline fosamil.

The study was not powered for comparative inferential efficacy analysis, and no efficacy endpoint was identified as primary. Clinical cure rates at test of cure (8 to 15 days after the end of therapy) in the MITT population were 94.4% (101/107) for ceftaroline fosamil and 86.5% (45/52) for the comparator, with a treatment difference of 7.9 (95% CI –1.2, 20.2).

Community acquired pneumonia

A study was conducted in paediatric patients aged 2 months to < 18 years with CAP. The primary objective was to evaluate the safety and tolerability of ceftaroline versus ceftriaxone, with 107 patients in the ceftaroline arm and 36 patients in the ceftriaxone arm (MITT population).

The CAP paediatric trial was a randomised, parallel-group, active controlled trial in paediatric patients 2 months to < 18 years of age. A total of 161 children with a diagnosis of CAP were enrolled in a randomised, multicentre, multinational, active controlled trial comparing ceftaroline fosamil with ceftriaxone. Patients with new or progressive pulmonary infiltrate(s) on chest radiography and signs and symptoms consistent with CAP including acute onset or worsening symptoms of cough, tachypnoea, sputum production, grunting, chest pain, cyanosis, or increased work of breathing with the need for hospitalisation and IV therapy were enrolled in the trial. Treatment duration was 5 to 14 days. A switch to oral therapy with amoxicillin clavulanate was allowed after Study Day 3. The Modified Intent-to-Treat (MITT) population included all randomised patients who received any amount of study drug with a confirmed diagnosis of CAP. The primary objective was to evaluate the safety and tolerability of ceftaroline fosamil. The study was not powered for comparative inferential efficacy analysis, and no efficacy endpoint was identified as primary.

Clinical cure rates at test of cure (8 to 15 days after final dose of study drug) in the MITT population were 87.9% (94/107) for ceftaroline fosamil and 88.9% (32/36) for the comparator, with a treatment difference of -1.0 (95% CI –11.5, 14.1).

5.2 Pharmacokinetic properties

Absorption

The C_{max} and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to 1000 mg. No appreciable accumulation of ceftaroline is observed following multiple IV infusions of 600 mg administered over 60 minutes every 8 or 12 hours for up to 14 days in healthy adults with normal renal function.

The systemic exposure (AUC), $T_{1/2}$, and clearance of ceftaroline were similar following administration of 600 mg ceftaroline fosamil in a volume of 50 mL to healthy adult subjects every 8 hours for 5 days as 5 minute or 60 minute infusions, and the T_{max} of ceftaroline occurred about 5 minutes after the end of the ceftaroline fosamil infusion for both infusion durations. The mean C_{max} (SD) of ceftaroline was 32.5 (4.82) mg/L for the 5 minute infusion duration (n=11) and 17.4 (3.87) mg/L for the 60 minute infusion duration (n=12).

Distribution

The plasma protein binding of ceftaroline is low (approximately 20%) and is not distributed into erythrocytes. The median steady-state volume of distribution of ceftaroline in healthy adult males following a single 600 mg IV dose of radiolabelled ceftaroline fosamil was 20.3 L, similar to extracellular fluid volume.

Metabolism

Ceftaroline fosamil (prodrug) is converted into the active ceftaroline in plasma by a phosphatase enzyme and concentrations of the prodrug are measurable in plasma primarily during IV infusion. Hydrolysis of the β-lactam ring of ceftaroline occurs to form the microbiologically inactive, open-ring metabolite, ceftaroline M-1. The mean plasma ceftaroline M-1 to ceftaroline AUC ratio following a single 600 mg IV infusion of ceftaroline fosamil in healthy subjects is approximately 20-30%.

In pooled human liver microsomes, metabolic turnover was low for ceftaroline, indicating that ceftaroline is not metabolised by hepatic CYP450 enzymes.

Excretion

Ceftaroline is primarily eliminated by the kidneys. Renal clearance of ceftaroline is approximately equal, or slightly lower than the glomerular filtration rate in the kidney, and *in vitro* transporter studies indicate that active secretion does not contribute to the renal elimination of ceftaroline.

The mean terminal elimination half-life of ceftaroline in healthy adults is approximately 2.5 hours.

Following the administration of a single 600 mg IV dose of radiolabelled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in faeces.

Special populations

Elderly (> 65 years)

Following administration of a single 600 mg IV dose of Zinforo, the pharmacokinetics of ceftaroline was similar between healthy elderly subjects (≥ 65 years of age) and healthy young adult subjects (18-45 years of age). There was a 33% increase in $AUC_{0-\infty}$ in the elderly that was mainly attributable to age-related changes in renal function. Zinforo dose adjustment is not required in elderly patients with creatinine clearance (CrCL) values above 50 mL/min.

Children and adolescents

Dose adjustments are required for children aged from 2 months to < 12 years and for adolescents aged 12 to < 18 years with bodyweight < 33 kg (see Section 4.2 Dose and method of administration). See Section 4.4 Special warnings and precautions for use, Paediatric use.

Gender

The pharmacokinetics of ceftaroline were similar between males and females. No dose adjustment is required based on gender.

Renal impairment

Dosage adjustments are required in adults, adolescents and children with creatinine clearance (CrCL) ≤ 50 mL/min (see Section 4.2 Dose and method of administration).

There is insufficient information to recommend dosage adjustments in adolescents with end stage renal disease (ESRD) aged from 12 to < 18 years and with bodyweight < 33 kg and in children with ESRD aged from 24 months to < 12 years. There is insufficient information to

recommend dosage adjustments in children aged < 24 months with moderate or severe renal impairment or ESRD.

Hepatic impairment

The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established. As ceftaroline does not appear to undergo significant hepatic metabolism, the systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment. Therefore, no dosage adjustment is recommended for patients with hepatic impairment.

5.3 Preclinical safety data

Genotoxicity

Ceftaroline fosamil and ceftaroline were clastogenic in an *in vitro* chromosomal aberration assay, however there was no evidence of mutagenic activity in Ames and mouse lymphoma assays. Furthermore, *in vivo* micronucleus assays in rat and mouse were negative.

Carcinogenicity

Carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine.

6.2 Incompatibilities

Zinforo must not be mixed with any other medications. Also refer to Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Vials: Store below 25°C. Store in the original package in order to protect from light.

After reconstitution

The powder for injection should be reconstituted and then diluted with diluents, listed in Section 6.6 Special precautions for disposal, immediately prior to use. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

After dilution

To reduce microbial hazard, Zinforo intravenous infusion should be administered as soon as practicable after preparation. If storage is necessary, hold at 2 to 8°C (Refrigerate. Do not freeze) for not more than 24 hours or not more than 6 hours at room temperature (including infusion time). The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 to 8°C, and up to 6 hours at room temperature.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.5 Nature and contents of container

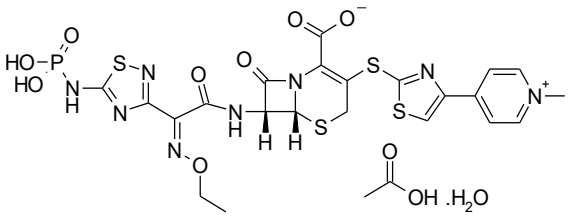
Available as 10 x 20 mL glass (Type 1) vials closed with a rubber (halobutyl) stopper and aluminium seal with blue flip-off cap.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



The chemical name of ceftaroline fosamil monoacetate monohydrate is (6R, 7R)-7-{(2Z)-2-(ethoxyimino)-2-[(5-phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monoacetate monohydrate.

The molecular formula of the solvate hydrate form is $C_{24}H_{27}N_8O_{11}PS_4$ and the molecular mass is 762.75.

The molecular formula of the solvent and water free form is $C_{22}H_{21}N_8O_8PS_4$ and the molecular mass is 684.68.

The solubility of ceftaroline fosamil in water is 8.6 mg/mL. Its solubility is increased in the IV infusion by inclusion of L-arginine as an alkalising agent. The pH of the IV infusion is in the range of 5.0 to 7.0.

Ceftaroline has one strongly acidic proton and one moderately acidic proton on the phosphoamino group (pKa 1.22 and 5.10), a strongly acidic carboxylic acid group (pKa 1.79) and a pKa associated with the secondary amide adjacent to the β-lactam (pKa 10.9).

CAS number

$C_{24}H_{27}N_8O_{11}PS_4$ (solvate hydrate form): 400827-55-6.

$C_{22}H_{21}N_8O_8PS_4$ (solvent and water free form): 229016-73-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine, Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

12 February 2013

10. DATE OF REVISION

28 January 2026

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of statement to specify that SCAR, TEN, DRESS and AGEP has been reported in patients taking ceftaroline.
8	Revision of Sponsor website address.

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