NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Zinforo® 600 mg powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftaroline fosamil acetic acid solvate monohydrate equivalent to 600 mg ceftaroline fosamil.

After reconstitution, 1 mL of the solution contains 30 mg of ceftaroline fosamil.

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 the designated susceptible bacteria (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties):

- 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.

4.2 Dose and method of administration

Dose

The recommended dosage, the frequency 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 normal renal function, 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[b] – 60 min every 12 hours
	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[b] – 60 mins every 8 hours[b]
	≥ 2 months to < 2 years	8 mg/kg	
	Birth to < 2 months[b]	6 mg/kg	60 mins every 8 hours
CAP/Duration of treatment is 5 – 7 days	Adults and adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	600 mg	5[b] – 60 min every 12 hours
	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[b] – 60 mins every 8 hours
	≥ 2 months to < 2 years	8 mg/kg	
	Birth to < 2 months[b]	6 mg/kg	60 mins every 8 hours
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 minutes infusion time and neonatal dose 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.] 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.

Dosage adjustments

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, Use in renal impairment, 5.2 Pharmacokinetic properties, Special population, 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 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[c] - 60 mins, every 12 hours
		≥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[c] – 60 mins, every 8 hours
		≥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	
	Children and adolescents 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 m2). 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 is 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]: 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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties, Special population, Hepatic impairment).

Special populations

Elderly (≥ 65 years)

No dosage adjustment is required for the elderly with creatinine clearance values > 50 mL/min (see Section 5.2 Pharmacokinetic properties, Special population, Elderly patients (≥ 65 years old)).

Paediatric population

Dose adjustments are required for neonates, infants, children or adolescents aged 12 to <18 years with bodyweight <33 kg (refer to Table 1 and 2 above).

Method of administration

Zinforo is administered by intravenous 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 solution for injection (0.45% sodium chloride and 2.5% dextrose)
- 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 intravenous 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 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, Zinforo IV 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 8ºC 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.

Hypersensitivity to the cephalosporin class of antibacterials.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterials, serious and occasionally fatal hypersensitivity reactions are possible (see Sections 4.3 Contraindications and 4.8 Undesirable effects).

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftaroline fosamil. Zinforo is contraindicated in patients with a history of hypersensitivity to cephalosporins. In addition, it is contraindicated in patients with a history of an immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of beta-lactam antibacterial agent (see Section 4.3 Contraindications). Zinforo should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or carbapenems.

If a severe allergic reaction occurs during treatment with Zinforo, the medicinal product should be discontinued and appropriate measures taken.

***Clostridium difficile*-associated diarrhoea**

Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftaroline fosamil 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 ceftaroline fosamil (see Section 4.8 Undesirable effects). In such circumstance, the discontinuation of therapy with ceftaroline fosamil and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products which inhibit intestinal peristalsis should not be given.

Non-susceptible organisms

Superinfections may occur during or following treatment with Zinforo.

Patients with pre-existing seizure disorder

As with other cephalosporins, seizures have occurred in ceftaroline toxicology studies at 7-25 times human ceftaroline C_{max} levels (see Section 5.3 Preclinical safety data). Clinical study experience with ceftaroline fosamil in patients with pre-existing seizure disorders is very limited. Therefore, Zinforo should be used with caution in this patient population.

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

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with cephalosporins. The incidence of DAGT 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). There was no evidence of haemolysis in any patient receiving ceftaroline fosamil who developed a positive DAGT. 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.

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. When SCAR is suspected, ceftaroline should be discontinued immediately and an alternative treatment should be considered.

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, necrotising 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.

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 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.

Paediatric population

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

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 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.

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 sections 4.4 Special warnings precautions for use and 4.9 Overdose).

4.5 Interactions with other medicines and other forms of interactions

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

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 or 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

Fertility

The effects of ceftaroline fosamil on fertility in humans have not been studied. Animal studies with ceftaroline fosamil do not indicate harmful effects with respect to fertility (see Section 5.3 Preclinical safety data).

Pregnancy

No clinical data on pregnancies are available for ceftaroline. Animal studies with ceftaroline fosamil do not indicate harmful effects with respect to fertility, pregnancy, parturition or postnatal development (see Section 5.3 Preclinical safety data). Zinforo should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.

Lactation

It is not known whether ceftaroline is excreted in human milk, but because many beta-lactams are excreted in breast milk, women who are breast-feeding should be treated with Zinforo only if clearly indicated. Interruption of breast-feeding is recommended.

4.7 Effects on ability to drive and use machinery

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., dizziness), which may influence the ability to drive and use machines following administration of Zinforo (see Section 4.8 Undesirable effects).

4.8 Undesirable effects

Adult

Pooled Phase 3 studies

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 incidences of treatment emergent adverse events in the pooled Phase 3 cSSTI and CAP studies were similar in ceftaroline and comparator groups (45.7% vs 46.7%, respectively). The most common adverse reactions occurring in ≥ 3% of patients treated with ceftaroline 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.

Additional Phase 3 studies

A study in Asia of 381 adult patients with CAP treated with ceftaroline (600 mg administered over 60 minutes every 12 hours) demonstrated that the safety profile of ceftaroline in these patients was similar to that observed in the pooled Phase 3 cSSTI and CAP studies.

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 (see below) and a greater incidence of DAGT seroconversion (see Section 4.4 Special warnings and precautions for use).

Tabulated list of adverse reactions

The following adverse reactions have been identified during clinical trials with ceftaroline. Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are derived from the adverse events observed in the pooled Phase 3 cSSTI and CAP studies and the Asia CAP study and are defined according to the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000).

Table 4: Frequency of adverse reactions by system organ class

Frequency	**System organ class**	**Event**
Very common (≥ 10%)	Investigations	Coombs Direct Test Positive (see section 4.4 Special warnings and precautions for use)
Common (≥ 1% and < 10%)	Nervous system disorders	Headache, dizziness
	Vascular disorders	Phlebitis
	Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain
	Hepatobiliary disorders	Increased transaminases
	Skin and subcutaneous tissue disorders	Rash, pruritus
	General disorders and administration site conditions	Pyrexia, infusion site reactions (erythema, phlebitis, pain)
Uncommon (≥ 0.1% and < 1%)	Infections and infestations	*Clostridium difficile* colitis(see section 4.4 Special warnings and precautions for use)
	Blood and lymphatic system disorders	Anaemia, leucopenia, neutropenia, thrombocytopenia
	Immune system disorders	Hypersensitivity/anaphylaxis (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use)
	Skin and subcutaneous tissue disorders	Urticaria

Frequency	System organ class	Event
	Renal and urinary disorders	Blood creatinine increased
	Investigations	Prothrombin time prolonged, international normalized ratio increased
Rare (≥ 0.01% and < 0.1%)	Blood and lymphatic system disorders	Agranulocytosis, eosinophilia

Post-marketing experience

Nervous system disorders: Encephalopathy.

Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia.

Description of selected adverse reactions

Skin and other subcutaneous tissue disorders

Rash

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%).

Severe cutaneous adverse reactions

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) have been reported in beta-lactam antibiotics. Also see section 4.4 Special warnings and precautions for use, Severe cutaneous adverse reactions.

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.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdosage

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 of overdose should follow standard medical practice.

Ceftaroline can be removed by haemodialysis; over a 4 hour dialysis period, approximately 74% of a given dose was recovered in the dialysate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other cephalosporins, ATC code: J01DI02.

The active moiety after Zinforo administration is ceftaroline.

Mechanism of action

In vitro studies have shown that ceftaroline is bactericidal and able to inhibit bacterial cell wall synthesis in methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin non-susceptible *Streptococcus pneumoniae* (PNSP) due to its affinity for the altered penicillin binding proteins (PBPs) found in these organisms. As a result, minimum inhibitory concentrations (MICs) of ceftaroline against a proportion of these organisms tested fall into the susceptible range (see Mechanisms of resistance section below).

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactam antimicrobial agents, 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 activities for ceftaroline.

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 beta-lactam agents.

Mechanisms of resistance

Ceftaroline is not active against strains of *Enterobacterales* producing extended-spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases or class C (AmpC) cephalosporinases.

Organisms that express these enzymes and which are therefore resistant to ceftaroline occur at very variable rates between countries and between healthcare facilities within countries. If ceftaroline is commenced before susceptibility test results are available then local information on the risk of encountering organisms that express these enzymes should be taken into consideration. Resistance may also be mediated by bacterial impermeability or drug efflux pump mechanisms. One or more of these mechanisms may co-exist in a single bacterial isolate.

Interaction with other antibacterial agents

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

Susceptibility testing breakpoints

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptibility testing are presented below.

Organisms	**MIC breakpoints (mg/L)**	
	Susceptible (S ≤)	**Resistant (R >)**
Staphylococcus aureus	1[1]	>2[2]
Streptococcus pneumoniae	0.25	0.25
Streptococcus Groups A, B, C, G	Note[3]	Note[3]
Haemophilus influenzae	0.03	0.03
Enterobacterales	0.5	0.5

Notes:

1: Refers to dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 12 hours using 1-hour infusions (see Section 4.2 Dose and method of administration). Note that: There are no clinical trial data regarding the use of ceftaroline to treat CAP due to S. aureus with ceftaroline MICs > 1 mg/L

2: Refers to dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 8 hours using 2-hour infusions to treat cSSTI (see Section 4.2 Dose and method of administration). S. aureus with ceftaroline MICs ≥ 4 mg/L are rare. PK-PD analyses suggest that dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 8 hours using 2-hour infusions may treat cSSTI due to S. aureus for which the ceftaroline MIC is 4 mg/L.

3: Infer susceptibility from susceptibility to benzylpenicillin.

Clinical efficacy against specific pathogens

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 infections

Gram-positive micro-organisms

Staphylococcus aureus (including methicillin-resistant strains)

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus group (includes *S. anginosus, S. intermedius* and *S. constellatus*)

Streptococcus dysgalactiae.

Gram-negative micro-organisms

Escherichia coli

Klebsiella pneumoniae

Klebsiella oxytocoa

Morganella morganii.

Community-acquired pneumonia

No cases of CAP due to MRSA were enrolled into the studies. The available clinical data cannot substantiate efficacy against penicillin non-susceptible strains of *S. pneumoniae*.

Gram-positive micro-organisms

Streptococcus pneumoniae.

Staphylococcus aureus (methicillin-susceptible strains only)

Gram-negative micro-organisms

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae.

Antibacterial activity against other relevant pathogens

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

Anaerobic micro-organisms

Gram-positive micro-organisms

Peptostreptococcus spp..

Gram-negative micro-organisms

Fusobacterium spp.

In vitro data indicate that the following species are not susceptible to ceftaroline:

Chlamydophila spp.

Legionella spp.

Mycoplasma spp.

Proteus spp.

Pseudomonas aeruginosa.

Clinical efficacy and safety

Complicated skin and soft tissue infections

A total of 1396 adults with documented complicated skin and soft tissue infections were enrolled in two identical randomised, multi-centre, multinational, double-blind studies (CANVAS 1 and CANVAS 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). Patients with deep/extensive cellulitis, a major abscess, a wound infection (surgical or traumatic), infected bites, burns or ulcers, or any lower extremity infection in patients with either pre-existing diabetes mellitus or peripheral vascular disease, were eligible for the studies. Treatment duration was 5 to 21 days. 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 in the table below.

Table 5: Clinical cure rates at TOC from two Phase 3 studies in cSSTI after 5 to 21 days of therapy

	Zinforo n/N (%)	**Vancomycin/Aztreonam n/N(%)**	**Treatment difference (2-sided 95% CI)**
CANVAS 1 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 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)

Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented below.

Table 6: Clinical cure rates by infecting pathogen from microbiologically evaluable patients with cSSTI (data from two integrated Phase 3 studies)

Organism	**Zinforo n/N (%)**	**Vancomycin/Aztreonam n/N(%)**
Gram-positive organisms		
Staphylococcus aureus	352/378 (93.1)	336/356 (94.4)
MSSA (methicillin-susceptible strains)	212/228 (93.0)	225/238 (94.5)
MRSA (methicillin-resistant strains)	142/152 (93.4)	115/122 (94.3)
Streptococcus pyogenes	56/56 (100.0)	56/58 (96.6)
Streptococcus agalactiae	21/22 (95.5)	18/18 (100.0)
Streptococcus dysgalactiae	13/13 (100.0)	15/16 (93.8)
Streptococcus anginosus group[a]	12/13 (92.3)	15/16 (93.8)
Gram-negative organisms		
Escherichia coli	20/21 (95.2)	19/21 (90.5)
Klebsiella pneumoniae	17/18 (94.4)	13/14 (92.9)
Morganella morganii	11/12 (91.7)	5/6 (83.3)
Klebsiella oxytocoa	10/12 (83.3)	6/6 (100.0)

[a] 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, multi-centre, 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 7: 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 8: 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)	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

A total of 1240 adults with a diagnosis of CAP were enrolled in two randomised, multi-centre, multinational, double-blind studies (FOCUS 1 and FOCUS 2) comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to ceftriaxone (1 g ceftriaxone 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. Patients with new or progressive pulmonary infiltrate(s) on chest radiography with clinical signs and symptoms consistent with CAP with the need for hospitalisation and intravenous therapy were enrolled in the studies. Treatment duration was 5 to 7 days. 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 clinically evaluable (CE) population included patients in the MITTE 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 MITTE populations in the table below.

Table 9: Clinical cure rates at TOC from the two Phase 3 studies in CAP after 5 to 7 days of therapy

	Zinforo n/N (%)	Ceftriaxone n/N(%)	Treatment difference (2-sided 95% CI)
FOCUS 1			
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			
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)

Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in the table below.

Table 10: Clinical cure rates by infecting pathogen from microbiologically evaluable patients with CAP (data from two integrated Phase 3 studies)

Organism	Zinforo n/N (%)	Ceftriaxone n/N(%)
Gram-positive organism		
Streptococcus pneumoniae	54/63 (85.7)	41/59 (69.5)
Staphylococcus aureus (methicillin-susceptible strains only)	18/25 (72.0)	14/25 (56.0)
Gram-negative organism		
Haemophilus influenzae	15/18 (83.3)	17/20 (85.0)
Haemophilus parainfluenzae	16/16 (100.0)	15/17 (88.2)
Escherichia coli	10/12 (83.3)	9/12 (75.0)
Klebsiella pneumoniae	13/13 (100.0)	10/12 (83.3)

In addition, a total of 771 adults with a diagnosis of CAP were enrolled in a randomised, multi-centre, double-blind study in Asia comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to ceftriaxone (2 g administered intravenously over 30 minutes every 24 hours). Treatment duration was 5 to 7 days. 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 (Tables 11 and 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/IV CAP in Asia.

Table 11: Clinical response at TOC - Non-inferiority (CE population)

	Number (%) of patients			
Clinical response	**Ceftaroline (N=247)**	**Ceftriaxone (N=231)**	**Difference**	**95% CI for difference**
Clinical cure	208 (84.2)	170 (73.6)	10.6	(3.3, 18.0)

	Number (%) of patients			
Clinical response	**Ceftaroline (N=247)**	**Ceftriaxone (N=231)**	**Difference**	**95% CI for difference**
Clinical failure	39 (15.8))	39 (15.8))		

Table 12: Clinical response at TOC (MITT population)

Population	Clinical response	Ceftaroline n (%)	Ceftriaxone n (%)	Difference	95% CI for difference
MITT	n	366	366		
	Clinical cure	293 (80.1)	244 (66.7	13.4	(7.0, 19.7)
	Clinical failure	50 (13.7)	89 (24.3)		
	Indeterminate	23 (6.3)	33 (9.0))		

Table 13: Clinical cure rates by infecting pathogen from microbiologically evaluable patients with CAP (data from Asia CAP study)

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

Children and adolescents

A study was conducted in paediatric patients aged 2 months to <18 years with cSSTI. The primary objective was to evaluate the safety and tolerability of ceftaroline versus vancomycin or cefazolin with or without aztreonam, with 107 patients in the ceftaroline arm and 52 patients in the comparator arms (MITT population).

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).

These studies were primarily designed to explore pharmacokinetics and safety and were not powered to demonstrate non-inferiority, however they were considered supportive of efficacy in paediatric patients.

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 intravenous infusions of 600 mg administered over 60 minutes every 8 or 12 hours 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 ceftaroline is not distributed into erythrocytes. The median steady-state volume of distribution of ceftaroline in healthy adult males following a single 600 mg intravenous dose of radiolabeled ceftaroline fosamil was 20.3 L, similar to the volume of extracellular fluid.

Metabolism

Ceftaroline fosamil (prodrug) is converted into the active ceftaroline in plasma by phosphatase enzymes and concentrations of the prodrug are measurable in plasma primarily during intravenous infusion. Hydrolysis of the beta-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 intravenous 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.

Elimination

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 intravenous dose of radiolabeled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in faeces.

Special populations

Elderly patients (≥ 65 years)

Following administration of a single 600 mg intravenous dose of ceftaroline fosamil, the pharmacokinetics of ceftaroline were 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 above 50 mL/min.

Renal impairment

Dosage adjustments are required in patients when creatinine clearance (CrCL) ≤ 50 mL/min (see Sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use, Use in renal impairment and 4.9 Overdosage).

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 has 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.

Paediatric population

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).

Gender

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

5.3 Preclinical safety data

The kidney was the primary target organ of toxicity in both the monkey and rat. Histopathologic findings included pigment deposition and inflammation of the tubular epithelium. Renal changes were not reversible but were reduced in severity following a 4 week recovery period.

Convulsions have been observed at relatively high exposures during single and multi-dose studies in both the rat and monkey (≥ 7 times to the estimated ceftaroline C_{max} level of a 600 mg twice a day).

Other important toxicologic findings noted in the rat and monkey included histopathologic changes in the bladder and spleen.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted.

Reproductive toxicology

Overall, no adverse effects on fertility or post-natal development were observed in the rat at up to 5 times the observed clinical exposure. When ceftaroline was administered during organogenesis, minor changes in fetal weight and delayed ossification of the interparietal bone were observed in the rat at exposures below that observed clinically. However, when ceftaroline was administered throughout pregnancy and lactation, there was no effect on pup weight or growth. Ceftaroline administration to pregnant rabbits resulted in an increased fetal incidence of angulated hyoid alae, a common skeletal variation in rabbit fetuses, at exposures similar to those observed clinically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and method of administration. Also refer to Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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 immediately prior to use with diluents listed in Section 4.2 Dose and method of administration. 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

20 mL glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap.

The medicinal product is supplied in packs of 10 vials.

6.6 Special precautions for disposal and other handling

The powder must be reconstituted with water for injections and the resulting concentrate diluted prior to use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, 1140, New Zealand.
Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

29 August 2013.

10. DATE OF REVISION OF TEXT

05 January 2021.

Summary of table of changes

Section changed	Summary of new information
4.8	Treatment Emergent Adverse Events
4.2, 4.8	Minor editorial change to table heading and footnote. Patient characteristics of trial participants in paediatric clinical safety trial

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