# Zinforo®

ceftaroline fosamil

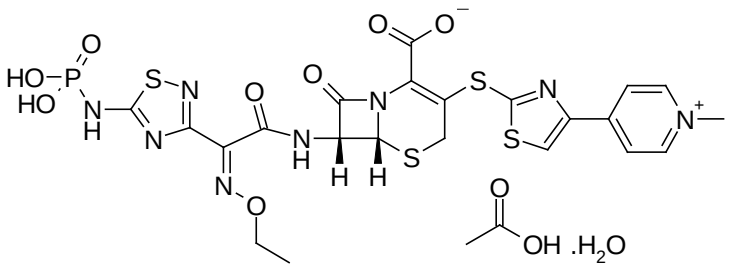
## PRODUCT INFORMATION

## NAME OF THE MEDICINE

Ceftaroline fosamil, as ceftaroline fosamil monoacetate monohydrate.

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 chemical structure of ceftaroline fosamil monoacetate monohydrate is:



| | solvate hydrate form | solvent and water free form |
|---|---|---|
| CAS number | 400827-55-6 | 229016-73-3 |
| Molecular formula | $C_{24}H_{27}N_8O_{11}PS_4$ | $C_{22}H_{21}N_8O_8PS_4$ |
| Relative molecular mass | 762.75 | 684.68 |

## DESCRIPTION

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

The solubility of ceftaroline fosamil in water is 8.6 mg/mL. Its solubility is increased in the intravenous (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).

Zinforo is a sterile, pyrogen-free pale yellowish-white to light yellow powder in a sterile vial. Each single use vial contains 600 mg of the prodrug ceftaroline fosamil (equivalent to 530 mg active ceftaroline), blended with 395 mg of L-arginine (for pH

adjustment). The powder is constituted for IV infusion (see *Dosage and administration – Constitution and compatibility*).

## PHARMACOLOGY

### Mechanism of action

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-nonsusceptible *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 *Enterobacteriaceae* 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 (eg 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 desirable, particularly when treating severe infections. 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 the *Clinical Trials* section 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 (also refer Table 3):*

- 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 oxytoca, Morganella morganii*

*Community acquired pneumonia (also refer Table 5):*

- Gram-positive aerobes
  *S. pneumoniae* (including cases with concurrent bacteraemia) and *S. aureus* (methicillin-susceptible strains only as MRSA was an exclusion criterion – refer *Clinical Trials* section 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 1 below.

**Table 1 *In vitro* activity from 2010 Australian bacterial surveillance**

| **Isolates (n)** | **Minimum inhibitory concentration (MIC) [mg/mL]** | |
|---|---|---|
| **Total (1523)** | **$MIC_{90}$** | **Range** |
| **Gram-positive aerobes** | | |
| *S. aureus* (466) | 0.5 | 0.06-2 |
| MSSA (335) | 0.25 | 0.06-0.5 |
| MRSA (131) | 1 | 0.25-2 |
| Coagulase negative *staphylococci* (8) | - | ≤0.008-0.5 |
| MSCoNS (2) | - | ≤0.008-0.12 |
| MRCoNS (6) | - | 0.25-0.5 |
| *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 |
| Penicillin-susceptible (121) | ≤0.008 | ≤0.008-0.015 |
| Penicillin-intermediate (34) | 0.06 | ≤0.008-0.12 |
| Penicillin-resistant (15) | 0.25 | 0.06-0.25 |
| **Gram-negative aerobes** | | |
| *Citrobacter* spp (40) | 32 | 0.06->32 |
| *Enterobacteriaceae* (265) | 2 | 0.015->16 |
| *Enterobacter* spp. (66) | >32 | 0.06->32 |
| *E. coli* (128) | 2 | 0.015->32 |
| ESBL phenotype (9) | - | 32 ->32 |
| non-ESBL phenotype (119) | 0.5 | 0.015->32 |
| *H. influenzae* (152) | 0.03 | ≤0.008-0.06 |
| β-lactamase positive (39) | 0.06 | ≤0.008-0.06 |
| β-lactamase negative (113) | 0.015 | ≤0.008-0.06 |
| *H. parainfluenzae* (9) | - | ≤0.008-0.015 |
| *K. pneumoniae* (52) | 0.5 | 0.03->32 |
| ESBL phenotype (4) | - | 4 ->32 |
| non-ESBL phenotype (48) | 0.5 | 0.03-1 |
| *K. oxytoca* (10) | >32 | 0.06->32 |
| ESBL phenotype (2) | - | >32 |
| non-ESBL phenotype (8) | - | 0.06-0.5 |

| Isolates (n) | | Minimum inhibitory concentration (MIC) [mg/mL] |
|---|---|---|
| **Total (1523)** | **$MIC_{90}$** | **Range** |
| *Moraxella catarrhalis* (36) | 0.12 | ≤0.008-0.5 |
| *Morganella morganii* (28) | >32 | 0.06->32 |
| **P. aeruginosa* (100) | >32 | 0.5->32 |
| *Serratia marcescens* (39) | 8 | 0.5->32 |

MSSA – methicillin-susceptible *S. aureus*; MRSA – methicillin-resistant *S. aureus*; MSCoNS – methicillin-susceptible coagulase negative *staphlococci*; MRCoNS – methicillin-resistant coagulase negative *staphlococci*; spp – species; ESBL – extended-spectrum β-lactamase; *not susceptible to ceftaroline

## Pharmacokinetics

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 12 hours for up to 14 days in healthy adults with normal renal function.

### *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 intravenous 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 intravenous 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 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 P450 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 intravenous dose of radiolabelled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in faeces.

### *Elderly patients*

Following administration of a single 600 mg intravenous 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 L/min.

### *Children (<18 years)*

Zinforo is not recommended for use in patients under 18 years of age (see *Precautions - Use in children*).

### *Gender*

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

### *Patients with renal impairment*

Dosage adjustment is required in patients with moderate renal impairment (CrCL >30 to 50 mL/min). There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤30 mL/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis.

### *Patients with 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.

## CLINICAL TRIALS

### Complicated skin and soft tissue infections (cSSTI)

The efficacy and safety of Zinforo in cSSTI was established in 2 identical randomised, multi-centre, 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 2) and was efficacious against cSSTI caused by MRSA and other common cSSTI pathogens (see Table 3). Clinical cure rates were similar across infection types and between patients with common co-morbidities (such as DM and PVD).

**Table 2 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) | 296/292 (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] |
| *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 3 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 oxytoca* | 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*;

### Community-acquired pneumonia (CAP)

The efficacy and safety of Zinforo in CAP was established in 2 randomized, multi-centre, 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 randomized 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 4) and was efficacious against CAP caused by *S. pneumoniae* and other common CAP pathogens (see Table 5).

**Table 4 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 5 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) |
| **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) |
| *Enterobacteriaceae:* | | | | |
| *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; Ceftriax. – Ceftriaxone; MDRSP – multi-drug resistant *S. pneumoniae*; MSSA – methicillin-susceptible *S. aureus;* N/A – not applicable; [a] presumed eradication and/or eradication of causative pathogen; *includes 2 patients with methicillin-resistant *S. aureus*

## INDICATIONS

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

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

## CONTRAINDICATIONS

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

Hypersensitivity to the cephalosporin class of antibiotics.

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

## PRECAUTIONS

### Hypersensitivity reactions

As with all β-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions are possible (see *Contraindications* and *Adverse 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 (eg anaphylactic reaction) previously to any type of β-lactam antibiotic, ceftaroline fosamil should not be administered (see *Contraindications*).

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

### *Clostridium 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 *Adverse effects*). In such circumstance, the discontinuation of therapy with Zinforo and the use of supportive measures together with the administration of specific treatment for *Clostridium 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.

### Patients with renal impairment

Clinical study experience with ceftaroline in patients with severe renal impairment and end stage renal disease (ESRD) is limited. Therefore, use of Zinforo is not recommended in these patient populations (see *Pharmacokinetics*).

### 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 10.7% (120/1117) in the pooled Phase III studies. 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.

### Appropriate use of antibiotics

Consideration should be given to official guidance on the appropriate use of antibiotics (see also *Dosage and Administration* and *Pharmacology – Susceptibility testing* sections).

### Non-susceptible organisms

Superinfections may occur as with other antibiotics.

### 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 – 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.

### Use in children

The safety and efficacy of Zinforo in children aged from birth to <18 years have not been established.

### Use in elderly

No dose adjustment is required in the elderly with CrCL values >50 mL/min (see *Pharmacokinetics* and *Dosage and Administration*).

### 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.

### Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## INTERACTIONS WITH OTHER MEDICINES

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 (eg probenecid) or with drugs that are substrates of these transporters would therefore not be expected.

## ADVERSE EFFECTS

### Clinical trial experience

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 pooled Phase 3 cSSTI and CAP trials were similar in Zinforo and comparator groups (45.7% vs 46.7%, respectively). The most common adverse reactions occurring in

≥3% of patients treated with Zinforo were diarrhoea, headache, nausea 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 CAP active comparator trials are listed in Table 6 regardless of causality.

**Table 6 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 |
| Pruritis* | 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.

The following adverse drug reactions have been observed with Zinforo in less than 1% of patients during the Phase 3 clinical trials.

**Table 7 Adverse drug reactions that occurred with Zinforo in <1% of patients during the Phase 3 cSSTI and CAP studies**

| Frequency | System organ class | Event |
|---|---|---|
| Uncommon (≥0.1 to <1%) | Blood & lymphatic system disorders | Anaemia; leucopenia; thrombocytopenia |
| | Immune system disorders | Hypersensitivity/anaphylaxis [a] |
| | Skin & subcutaneous disorders | Urticaria |
| | Infections and infestations | *Clostridium difficile* colitis [b] |
| | Investigations | Prothrombin time prolonged; international normalized ratio increased |
| | Renal & urinary disorders | Blood creatinine increased |

[a] see *Contraindications* and *Precautions*

[b] see *Precautions*

The development of a positive Coombs test may occur during the treatment with cephalosporins, including Zinforo (see *Precautions*).

## DOSAGE AND ADMINISTRATION

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 may contribute to the empiric selection of therapy.

### Adults (18 years and older)

The recommended dosage of Zinforo is 600 mg administered every 12 hours by intravenous infusion over 60 minutes. The duration of therapy should be guided by the type of infection to be treated, its severity and the patient's clinical response.

Recommended dosage and administration by infection is as follows:

**Table 8 Adult dosage and administration recommendations**

| Infection | Dosage | Frequency | Infusion time (min) | Recommended duration of antimicrobial treatment |
|---|---|---|---|---|
| Complicated skin & soft tissue infections | 600 mg | every 12 hours | 60 | 5-14 days |
| Community-acquired pneumonia | 600 mg | every 12 hours | 60 | 5-7 days |

### *Patients with renal impairment*

The dose should be adjusted in patients with renal impairment when creatinine clearance (CrCl) levels are >30 to ≤50 mL/min, as shown below (see *Precautions* and *Pharmacokinetics*).

| Creatinine clearance (mL/min) | Dosage | Frequency | Infusion time (min) | Recommended duration of antimicrobial treatment |
|---|---|---|---|---|
| >30 to ≤50 | 400 mg | every 12 hours | 60 | Refer above |

There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCl ≤30 mL/min) and end-stage renal disease, including patients undergoing haemodialysis.

### *Patients with hepatic impairment*

No dosage adjustment is considered necessary in patients with hepatic impairment (see *Pharmacokinetics*).

### *Elderly patients*

No dosage adjustment is required for the elderly with CrCL values above 50 mL/min (see *Pharmacokinetics*).

### Children (<18 years)

The safety and efficacy in children have not yet been established.

### Constitution and compatibility

The powder must be constituted with water for injections and the resulting constituted solution must then be immediately diluted prior to use. The constituted solution is a pale yellow solution that is free of any particles.

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

Zinforo powder should be constituted with 20 mL of sterile water for injections. The resulting constituted 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.*

Routinely, a 250 mL infusion bag should be used to prepare the infusion and only in exceptional patients for whom there could be great concern over volumes infused should a 50 mL or 100 mL infusion bag be used.

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

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

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

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

### *Stability after constitution and dilution*

*After constitution*

The constituted vial should be used immediately.

*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 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.

## 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 under such circumstances should follow local standard medical practice.

Ceftaroline can be partially removed by haemodialysis.

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

## PRESENTATION AND STORAGE CONDITIONS

Zinforo vials contain 600 mg of the prodrug ceftaroline fosamil (equivalent to 530 mg active ceftaroline), blended with 395 mg of L-arginine (for pH adjustment).

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

### Storage conditions

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

Constituted and diluted product: See *Dosage and administration – Constitution and compatibility*.

## NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

## POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

12th February 2013

## DATE OF MOST RECENT AMENDMENT

N/A