# Zinforo® 600 mg Powder for Concentrate for Solution for Infusion

ceftaroline fosamil

## 1. NAME OF THE MEDICINAL PRODUCT

Zinforo® (ceftaroline fosamil) powder for concentrate for solution for infusion, IV, 600 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftaroline fosamil 600 mg equivalent to ceftaroline 530 mg.

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion. A pale yellowish-white to light yellow powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Zinforo is indicated for the treatment of the following infections caused by susceptible isolates of the designated microorganisms:

- Complicated skin and soft tissue infections (cSSTI)
- Community-acquired pneumonia (CAP)

Zinforo is indicated in neonates, infants, children, adolescents and adults.

### 4.2 Posology and method of administration

Posology

The recommended durations of treatment are 5-14 days for cSSTI and 5-7 days for CAP.

**Table 1 Dosage in adults with normal renal function, creatinine clearance (CrCL) >50 mL/min**

| **Indications** | **Posology (mg/infusion)** | **Infusion time (minutes)/Frequency** |
|---|---|---|
| Standard dose[a]<br><br>Complicated skin and soft tissue infections (cSSTI)<br><br>Community-acquired pneumonia (CAP) | 600 mg | 5 – 60[b]/every 12 hours |
| High dose[b]<br><br>cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[c] | | 120/every 8 hours |

[a] For patients with supranormal renal clearance receiving the standard dose, an infusion time of 60 minutes may be preferable.

[b] Infusion times of less than 60 minutes and high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See sections 4.4 and 5.1.

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

**Table 2 Dosage in paediatric patients with normal renal function, creatinine clearance (CrCL) >50 mL/min***

| **Indications** | **Age group** | **Posology (mg/infusion)** | **Infusion time (minutes)/Frequency** |
|---|---|---|---|
| Standard dose[a]<br><br>Complicated skin and soft tissue infections (cSSTI)<br><br>Community-acquired pneumonia (CAP) | Adolescents aged from 12 to <18 years with bodyweight ≥33 kg | 600 mg | 5 – 60[b]/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 – 60[b]/every 8 hours |
| | Infants ≥2 months to <2 years | 8 mg/kg | 5 – 60[b]/every 8 hours |
| | Neonates from birth to <2 months[b] | 6 mg/kg | 60/every 8 hours |
| High dose[b]<br><br>cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[c] | Children and adolescents aged from ≥2 years to <18 years | 12 mg/kg to a maximum of 600 mg | 120/every 8 hours |
| | Infants ≥2 months to <2 years | 10 mg/kg | 120/every 8 hours |

[a] For patients with supranormal renal clearance receiving the standard dose, an infusion time of 60 minutes may be preferable.

[b] Infusion times of less than 60 minutes, neonatal and high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See sections 4.4 and 5.1.

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

* Calculated using the Schwartz formula (in mL/min/1.73 $m^2$) for paediatric patients.

Special populations

*Elderly*
No dosage adjustment is required for the elderly with creatinine clearance values >50 mL/min (see section 5.2).

*Renal impairment*
The dose should be adjusted when creatinine clearance (CrCL) is ≤50 mL/min, as shown in Tables 3 and 4 (see sections 4.9 and 5.2). The recommended durations of treatment are 5-14 days for cSSTI and 5-7 days for CAP.

**Table 3 Dosage in adults with impaired renal function, creatinine clearance (CrCL) ≤50 mL/min**

| **Indications** | **Creatinine clearance (mL/min)[a]** | **Posology (mg/infusion)** | **Infusion time (minutes)/Frequency** |
|---|---|---|---|
| Standard dose<br><br>Complicated skin and soft tissue infections (cSSTI)<br><br>Community-acquired pneumonia (CAP) | >30 to ≤50 | 400 mg | 5 – 60[c]/every 12 hours |
| | ≥15 to ≤30 | 300 mg | |
| | ESRD, including haemodialysis[b] | 200 mg | |
| High dose[c]<br><br>cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[d] | >30 to ≤50 | 400 mg | 120/every 8 hours |
| | ≥15 to ≤30 | 300 mg | |
| | ESRD, including haemodialysis[b] | 200 mg | |

[a] Calculated using the Cockcroft-Gault formula for adults. 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] Infusion times of less than 60 minutes and high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See sections 4.4 and 5.1.
[d] For treatment of *S. aureus* for which the ceftaroline MIC is ≤1 mg/L, the standard dose is recommended.

Dose recommendations for neonates, infants and children and adolescents are based on pharmacokinetic (PK) modelling.

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 2 to 12 years with end-stage renal disease (ESRD).

There is insufficient information to recommend dosage adjustments in paediatric patients <2 years with moderate or severe renal impairment or ESRD.

**Table 4 Dosage in paediatric patients with impaired renal function, creatinine clearance (CrCL ≤50 mL/min)**

| **Indications** | **Age group** | **Creatinine clearance (mL/min)[a]** | **Posology (mg/infusion)** | **Infusion time (minutes)/Frequency** |
|---|---|---|---|---|
| <u>Standard dose</u><br><br>Complicated skin and soft tissue infections (cSSTI)<br><br>Community-acquired pneumonia (CAP) | Adolescents aged from 12 to <18 years with bodyweight ≥33 kg | >30 to ≤50 | 400 mg | 5 – 60[c]/every 12 hours |
| | | ≥15 to ≤30 | 300 mg | |
| | | ESRD, including haemodialysis[b] | 200 mg | |
| | Adolescents aged from 12 years to <18 years bodyweight <33 kg **and** children ≥2 years to <12 years | >30 to ≤50 | 8 mg/kg to a maximum of 300 mg | 5 – 60[c]/every 8 hours |
| | | ≥15 to ≤30 | 6 mg/kg to a maximum of 200 mg | |
| <u>High dose</u>[c]<br><br>cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[d] | Children and adolescents aged from ≥2 years to <18 years | >30 to ≤50 | 10 mg/kg to a maximum of 400 mg | 120/every 8 hours |
| | | ≥15 to ≤30 | 8 mg/kg to a maximum of 300 mg | |

[a] Calculated using the 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] Infusion times of less than 60 minutes and high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses only. See sections 4.4 and 5.1.

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

*Hepatic impairment*

No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2).

<u>Method of administration</u>

Intravenous use. Zinforo is administered by intravenous infusion over 5 to 60 minutes for standard dose or 120 minutes for high dose (for cSSTI caused by *S. aureus* with MIC of 2 or 4 mg/L to ceftaroline) in infusion volumes of 50 mL, 100 mL or 250 mL (see section 6.6). Infusion related reactions (such as phlebitis) can be managed by prolonging the infusion duration.

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

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of its 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 and 4.8).

Severe cutaneous adverse reactions (SCARs), 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).

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

If a severe allergic reaction or SCAR occurs, the medicinal product 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 ceftaroline fosamil (see section 4.8). 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**
As with other cephalosporins, seizures have occurred in ceftaroline toxicology studies at 7-25 times human $C_{max}$ levels (see section 5.3). 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.

**Direct antiglobulin test (Coombs test) seroconversion**
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 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). 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.

**Non-susceptible organisms**
Superinfections may occur as with other antibacterial agents.

**cSSTI caused by *S. aureus* with an MIC >1 mg/L to ceftaroline**
There are limited clinical 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 to 4 for the treatment of cSSTI caused by *S. aureus* with ceftaroline MIC of 2 mg/L or 4 mg/L are based on pharmacokinetic-pharmacodynamic modelling and simulation (see sections 4.2 and 5.1). Zinforo should not be used to treat cSSTI due to *S. aureus* for which the ceftaroline MIC is >4 mg/L.

**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 2 for paediatric patients <2 months of age is based on pharmacokinetic-pharmacodynamic modelling and simulation (see section 4.2).

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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 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 Pregnancy and lactation

**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). 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 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).

## 4.8 Undesirable effects

**Pooled Phase III studies**
Four Phase 3 clinical trials (two in cSSTI and two in CAP) included 1305 adult patients treated with ceftaroline fosamil (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, and pruritus, and were generally mild or moderate in severity.

**Additional Phase III studies**
A study (Asia CAP) in Asia of 381 adult patients with CAP treated with ceftaroline fosamil (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 ceftaroline fosamil (600 mg administered over 120 minutes every 8 hours). The most common adverse reactions occurring in ≥3% of patients treated with ceftaroline fosamil were nausea, headache, and rash. The safety profile of ceftaroline was similar to that observed in previous pooled Phase III 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).

The safety assessment in paediatric patients is based on the safety data from 2 trials in which 227 patients aged from 2 months to 17 years with cSSTI or CAP received ceftaroline fosamil. Overall, the safety profile in these 227 patients was similar to that observed in the adult population.

In addition, the safety assessment in neonates and infants (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 ceftaroline fosamil.

The following adverse reactions have been identified during clinical trials and post marketing experience with ceftaroline fosamil. Adverse reactions are classified according to frequency and System Organ Class. 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 (≥10%), Common (≥1%, <10%), Uncommon (≥0.1%, <1%), Rare (≥0.01%, <0.1%), Not known (cannot be estimated from the available data).

**Table 5 Frequency of adverse reactions in clinical trials**

| **Frequency** | **System organ class** | **Event** |
|---|---|---|
| Very common (≥10%) | Investigations | Coombs Direct Test Positive (see section 4.4) |
| Common (≥1% and <10%) | Gastrointestinal disorders | Diarrhoea, nausea, vomiting, abdominal pain |
| | Nervous system disorders | Headache, dizziness |
| | Skin and subcutaneous tissue disorders | Rash, pruritus |
| | Hepatobiliary disorders | Increased transaminases |
| | Vascular disorders | Phlebitis |
| | General disorders and administration site conditions | Pyrexia, infusion site reactions (erythema, phlebitis, pain) |
| Uncommon (≥0.1% and <1%) | Blood and lymphatic system disorders | Anaemia, leucopenia, thrombocytopenia |
| | Immune system disorders | Hypersensitivity/anaphylaxis (see sections 4.3 and 4.4) |
| | Skin and subcutaneous tissue disorders | Urticaria |
| | Infections and infestations | *Clostridium difficile* colitis (see section 4.4) |
| | Investigations | Prothrombin time prolonged, international normalised ratio increased |
| | Renal and urinary disorders | Blood creatinine increased |
| | Nervous system disorders | Encephalopathy* |
| Rare (≥0.01% and <0.1%) | Blood and lymphatic system disorders | Eosinophilia |
| Not known | Blood and lymphatic system disorders | Agranulocytosis*, neutropenia* |
| | Respiratory, thoracic and mediastinal disorders | Eosinophilic pneumonia* |
| | Skin and subcutaneous tissue disorders | Stevens-Johnson syndrome*, toxic epidermal necrolysis*, drug reaction with eosinophilia and systemic symptoms*, acute generalised exanthematous pustulosis* |

* Adverse Drug Reaction (ADR) identified post marketing.

**Description of selected adverse reactions**

*Rash*
Rash was observed at a common frequency in the pooled Phase III studies in cSSTI with administration of ceftaroline fosamil 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 ceftaroline fosamil every 8 hours (COVERS) was very common (18.5%).

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

## 4.9 Overdose

Intentional overdosing of ceftaroline fosamil is unlikely. Limited data in patients receiving higher than recommended ceftaroline fosamil dosages show similar adverse reactions as observed in the patients receiving recommended dosages. Treatment under such circumstances should follow local standard medical practice.

*Patients with renal impairment*
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 4.2).

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

**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 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.

**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). One or more of these mechanisms may co-exist in the same bacterium.

**Interaction with other antimicrobials**
*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).

**Clinical efficacy against specific pathogens**
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.

This list is provided based on clinical efficacy and pharmacokinetic/pharmacodynamic data from clinical studies. Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to ceftaroline *in vitro*.

| **Susceptibility** |
|---|
| Complicated skin and soft tissue infections<br><br>Gram-positive organisms<br>• *Staphylococcus aureus* (including methicillin-resistant strains)<br>• *Streptococcus pyogenes*<br>• *Streptococcus agalactiae*<br>• *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)<br>• *Streptococcus dysgalactiae*<br><br>Gram-negative organisms<br>• *Escherichia coli*<br>• *Klebsiella pneumoniae*<br>• *Klebsiella oxytoca*<br>• *Morganella morganii* |
| Community-acquired pneumonia<br><br>Gram-positive organisms<br>• *Streptococcus pneumoniae*<br>• *Staphylococcus aureus* (methicillin-susceptible strains only)<br><br>Gram-negative organisms<br>• *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 Gram-positive organisms
- *Peptostreptococcus* species

Anaerobic Gram-negative organisms
- *Fusobacterium* species

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

**Susceptibility testing interpretive criteria (breakpoints)**
European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are based on the dosages below. Alternative dosing regimens may result in equivalent exposure. The table should not be used as a guidance for dosing in clinical practice as dosages can vary widely by indication. It does not replace specific national, regional or local dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

The EUCAST Breakpoint Tables v. 14.0 2024 indicates that the standard dosage on which breakpoints are based is 600 mg twice daily intravenously over 60 minutes. A higher dosage (600 mg three times daily intravenously over 120 minutes) may be indicated in some cases. For inhibition zone determination, the disks contain 5 µg of ceftaroline.

The EUCAST breakpoints for ceftaroline are listed in the following table:

| **Pathogen** | **Minimum Inhibitory Concentration (mg/L)** | | **Disk Diffusion Inhibition Zone (mm Diameter)** | |
|---|---|---|---|---|
| | **S≤** | **R>** | **S≥** | **R<** |
| Enterobacterales | 0.5 | 0.5 | 23 | 23 |
| *Staphylococcus aureus* (indications other than pneumonia) | 1[1] | 2[2] | 20 | 17 |
| *Staphylococcus aureus* (pneumonia) | 1 | 1 | 20 | 20 |
| *Streptococcus* Groups A, B, C, G* | - | - | - | - |
| *Streptococcus pneumoniae* | 0.25 | 0.25 | ** | - |
| *Haemophilus influenzae* | 0.03 | 0.03 | *** | - |

Source: EUCAST Clinical Breakpoint Table v. 14.0, 1 January 2024.
S = Susceptible. R = Resistant.

* The susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.
** The oxacillin 1 µg disk diffusion screening test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin zone diameter ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). A zone diameter of ≥9 mm indicates susceptibility to meropenem for non-meningitis isolates.
*** The benzylpenicillin 1 unit disk diffusion screening test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (zone diameter ≥12 mm) all carbapenems for which clinical breakpoints are available, including those with "Note", can be reported susceptible without further testing except for cefuroxime oral, which if reported, should be reported "susceptible, increased exposure" (I).

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). 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). *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.

Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

Quality control ranges for EUCAST susceptibility breakpoints are listed in the following table:

| **Quality control ranges for ceftaroline fosamil to be used in conjunction with EUCAST susceptibility test interpretive criteria** | | |
|---|---|---|
| | **Minimal Inhibitory Concentration (mg/L of Ceftaroline)** | **Disk Diffusion Inhibition Zone (mm Diameter)** |
| **Quality Control Strain** | | |
| *Staphylococcus aureus* ATCC 29213 | 0.125-0.5 | 24-30 |
| *Streptococcus pneumoniae* ATCC 49619 | 0.008-0.03 | - |
| *Haemophilus influenzae* ATCC 49766 | 0.004-0.016 | - |
| *Escherichia coli* ATCC 25922 | 0.03-0.12 | 24-30 |

Source: The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 14.0, 2024.

## 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 ceftaroline fosamil (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 6 Clinical cure rates at TOC from two Phase 3 studies in cSSTI after 5 to 21 days of therapy**

| | **Ceftaroline 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 7 Clinical cure rates by infecting pathogen from microbiologically evaluable patients with cSSTI (data from two integrated Phase 3 studies)**

| **Organism** | **Ceftaroline 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 oxytoca* | 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 $cm^2$, 40% had SIRS, and 61% had elevated CRP (>50 mg/L). 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) |

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

**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*

Paediatric studies

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, multi-centre, 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 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 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 ceftaroline fosamil (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 10 Clinical cure rates at TOC from the two Phase 3 studies in CAP after 5 to 7 days of therapy**

| | **Ceftaroline 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 11 Clinical cure rates by infecting pathogen from microbiologically evaluable patients with CAP (data from two integrated Phase 3 studies)**

| **Organism** | **Ceftaroline n/N (%)** | **Ceftriaxone n/N (%)** |
|---|---|---|
| **Gram-positive organism** | | |
| *Streptococcus pneumoniae* | 54/63 (85.7) | 41/59 (69.5) |
| *Staphylococcus aureus* MSSA (methicillin-susceptible) | 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) |

Asia CAP study

A total of 771 adults with a diagnosis of CAP were enrolled in a randomised, multi-centre, double-blind study in Asia comparing ceftaroline fosamil (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 12 and 13). 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 12 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) |
| Clinical failure | 39 (15.8) | 61 (26.4) | | |

**Table 13 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 14 Clinical cure rates by infecting pathogen from microbiologically evaluable patients with CAP (data from Asia CAP study)**

| **Organism** | **Ceftaroline 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) |

Paediatric studies

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, multi-centre, 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 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

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 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 (SD) $C_{max}$ 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 radiolabelled 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.

**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.

**Special populations**

*Patients with renal impairment*
Dosage adjustments are required in adults, adolescents and children with CrCL ≤50 mL/min (see section 4.2).

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 2 to <12 years. There is insufficient information to recommend dosage adjustments in paediatric patients aged <2 years with moderate or severe renal impairment or ESRD.

*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.

*Elderly patients*
Following administration of a single 600 mg intravenous dose of ceftaroline fosamil, 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 slight 33% increase in $AUC_{0-\infty}$ in the elderly that was mainly attributable to age-related changes in renal function. Ceftaroline dose adjustment is not required in elderly patients with creatinine clearance above 50 mL/min.

*Paediatric patients*
Dose adjustments are required for neonates, infants, children and adolescents with bodyweight <33 kg (see section 4.2).

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

*Race*
Race was evaluated as a covariate in a population pharmacokinetic analysis on data from the clinical studies. No significant differences in ceftaroline pharmacokinetics were observed in Caucasian, Hispanic, Black, Asian or other subjects. No dosage adjustment is recommended based on race.

## 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 $C_{max}$ 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.

Genetic toxicology
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 studies have not been conducted.

Reproductive toxicology
Reproductive studies in pregnant rabbits resulted in an increased foetal incidence of angulated hyoid alae, a common skeletal variation in rabbit foetuses, at exposures similar to 600 mg twice daily in humans. In the rat, no adverse effects were observed on embryofoetal development, fertility or postnatal development.

Juvenile toxicity
Intravenous bolus dosing of ceftaroline fosamil to suckling rats from post-natal day 7 to 20 was well tolerated at plasma exposure approximately 2-fold higher than those for paediatric patients.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

L-arginine

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

Dry powder: 3 years.

After reconstitution:
The reconstituted vial should be used immediately (see section 6.6 for details).

After dilution:
Once the intravenous solution is prepared with diluents listed in section 6.6 it should be administered within 6 hours of preparation. The chemical and physical in-use stability has been demonstrated for up to 12 hours at 2-8°C. Once removed from refrigeration to room temperature (below 25°C), the diluted product must be used within 6 hours.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of

the user and would normally not be longer than 12 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from light.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

## 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 must then be immediately diluted prior to use. The reconstituted 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 reconstituted with 20 mL of sterile water for injections. The resulting 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

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 paediatric patients will vary according to the weight of the child. The infusion solution concentration during preparation and administration should not exceed 12 mg/mL ceftaroline fosamil.

Each vial is for single use only.

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

## 7. PRODUCT OWNER

Pfizer Ireland Pharmaceuticals Unlimited Company,
Operations Support Group, Ringaskiddy
County Cork, Ireland.

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