1. NAME OF THE MEDICINAL PRODUCT

Zinforo 600 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

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 in neonates, infants, children, adolescents and adults (see sections 4.4 and 5.1):

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Dosage in adults and paediatric patients

The recommended dosage of Zinforo is 600 mg administered every 12 hours by intravenous infusion over 5 to 60 minutes (standard dose), with appropriate reductions for paediatric patients (see Table 1). The duration of treatment should be guided by the type of infection to be treated, its severity, and the patient's clinical response.

For the treatment of cSSTI confirmed or suspected to be caused by *Staphylococcus aureus* (*S. aureus*) with a Minimum Inhibitory Concentration (MIC) <2 mg/L to ceftaroline, the dose of Zinforo is 600 mg administered every 12 hours by intravenous infusion over 5 to 60 minutes (standard dose), with appropriate reductions for paediatric patients (see Table 1).

For the treatment of patients with cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline, the dose of Zinforo is 600 mg administered every 8 hours by intravenous infusion over 120 minutes (high dose), with appropriate reductions for paediatric patients (see Table 1).

Table 1 Dosage in patients with Creatinine Clearance (CrCL) >50 mL/min*

Indications / Recommended duration of treatment (days)	Age group	Posology	Infusion time (minutes)[a] / Frequency
Standard dose cSSTI[b] / 5 – 14 CAP[c] / 5 – 7	Adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg	600 mg	5 – 60 / every 12 hours
	Adolescents aged from 12 years to <18 years with bodyweight <33 kg and children ≥2 years to <12 years	12 mg/kg to a maximum of 400 mg	5 – 60 / every 8 hours
	≥2 months to <2 years	8 mg/kg	5 – 60 / every 8 hours
	Birth to < 2 months[d]	6 mg/kg	60 / every 8 hours
High dose cSSTI[b] confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[d] / 5 – 14	Adults	600 mg	120 / every 8 hours
	Adolescents and children aged from ≥2 years to < 18 years	12 mg/kg to a maximum of 600 mg	120 / every 8 hours
	≥2 months to <2 years	10 mg/kg	120 / every 8 hours

a The 5 minute infusion time is based on pharmacokinetic and pharmacodynamic analyses.
b Complicated skin and soft tissue infections (cSSTI) indication.
c Community-acquired pneumonia (CAP) indication.
d Neonatal and high dose recommendations are based on pharmacokinetic and pharmacodynamic analyses. See sections 4.4 and 5.1.
* Calculated using the Cockcroft-Gault formula for adults and Schwartz formula (in mL/min/1.73 m^2) for paediatric patients.

Special populations

Patients with renal impairment

The dose should be adjusted when creatinine clearance (CrCL) is ≤50 mL/min, as shown in Table 2. Dose recommendations for children and adolescents are based on PK modelling. End Stage Renal Disease (ESRD) patients can only be dosed as in Table 2.

For ESRD, there is insufficient information to recommend dosage adjustments in adolescents aged from 12 to <18 years with bodyweight <33 kg and in children aged from 2 to 12 years. There is insufficient information to recommend dosage adjustments in paediatric patients <2 years with moderate or severe renal impairment or ESRD.

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

Indications / Recommended duration of treatment (days)	Age group	Creatinine clearance (mL/min)[a]	Posology	Infusion time (minutes)[b] / Frequency
Standard dose cSSTI[c] / 5 – 14 CAP[d] / 5 – 7	Adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg	>30 to ≤50	400 mg	5 – 60 / every 12 hours
		≥15 to ≤30	300 mg	
		ESRD, including haemodialysis[f]	200 mg	

Indications / Recommended duration of treatment (days)	**Age group**	**Creatinine clearance (mL/min)[a]**	**Posology**	**Infusion time (minutes)[b] / Frequency**
	Adolescents aged from 12 years to <18 years with bodyweight <33 kg and children ≥2 years to < 12 years	>30 to ≤50	8 mg/kg to a maximum of 300 mg	5 – 60 / every 8 hours
		≥15 to ≤30	6 mg/kg to a maximum of 200 mg	
High dose cSSTI[c] confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[e] / 5 – 14	Adults	>30 to ≤50	400 mg	120 / every 8 hours
		≥15 to ≤30	300 mg	
		ESRD, including haemodialysis[f]	200 mg	
	Adolescents and children 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 Cockcroft-Gault formula for adults and Schwartz formula for paediatric patients (in mL/min/1.73 m^2). Dose is based on CrCL. CrCL should be closely monitored and the dose adjusted according to changing renal function.
b The 5 minute infusion time is based on pharmacokinetic and pharmacodynamic analyses.
c Complicated skin and soft tissue infections (cSSTI) indication.
d Community-acquired pneumonia (CAP) indication.
e Based on pharmacokinetic and pharmacodynamic analyses. See sections 4.4 and 5.1.
f Ceftaroline is haemodialyzable; thus Zinforo should be administered after haemodialysis on haemodialysis days.

Patients with hepatic impairment

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

Elderly patients

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

Reconstitution and compatibility

See section 6.6.

4.3 Contraindications

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

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

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.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. 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 anti-bacterial 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). There was no evidence of haemolysis in any patient receiving ceftaroline fosamil who developed a positive DAGT.

Non-susceptible organisms

Superinfections may occur as with other antibacterial agents.

Limitations of the clinical data

There is no experience with ceftaroline in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease (e.g. cystic fibrosis, see section 5.2), those with PORT Risk Class V, and/or CAP requiring ventilation at presentation, CAP due to methicillin-resistant *S. aureus* or patients requiring intensive care. Caution is advised when treating such patients.

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

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

There are limited clinical data for ceftaroline in treating cSSTI in adults caused by *S. aureus* with an MIC >1 mg/L to ceftaroline and there are no clinical data for treating *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline. Therefore, the recommended dosages of Zinforo to treat cSSTI caused by *S. aureus* with an MIC >1 mg/L to ceftaroline are based on pharmacokinetic/pharmacodynamic modelling and simulation (see section 4.2).

Paediatric patients < 2 months of age

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

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 Fertility, 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 e.g. dizziness 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%versus 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.

Table 3 Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organisations of Medical Science (CIOMS) Frequency Category listed in Order of Decreasing Medical Seriousness or Clinical Importance Within each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Infections and infestations			*Clostridium difficile* colitis			

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Thrombocytopenia, Leucopenia, Anaemia	Eosinophilia*		Agranulocytosis*, Neutropenia*
Immune system disorders			Hypersensitivity/anaphylaxis			
Nervous system disorders		Headache, Dizziness	Encephalopathy*			
Vascular disorders		Phlebitis				
Respiratory, thoracic and mediastinal disorders						Eosinophilic pneumonia*
Gastrointestinal disorders		Diarrhoea, Nausea, Vomiting, Abdominal pain				
Hepatobiliary disorders		Increased transaminases				
Skin and subcutaneous tissue disorders		Rash, Pruritus	Urticaria			
Renal and urinary disorders			Blood creatinine increased			
General disorders and administration site conditions		Infusion site reactions (erythema, phlebitis, pain), Pyrexia				
Investigations	Coombs Direct Test Positive		International normalized ratio increased, Prothrombin time prolonged			

* 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, other cephalosporins, ATC code: J01DI02

The active moiety after ceftaroline fosamil administration is ceftaroline.

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 non-susceptible *Streptococcus pneumoniae* (PNSP) due to its high 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.

Resistance

Ceftaroline is not active against strains of *Enterobacterales* producing extended-spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases or class C (AmpC) cephalosporinases. Organisms that express these enzymes and which are therefore resistant to ceftaroline occur at very variable rates between countries and between healthcare facilities within countries. If ceftaroline is commenced before susceptibility test results are available then local information on the risk of encountering organisms that express these enzymes should be taken into consideration. Resistance may also be mediated by bacterial impermeability or drug efflux pump mechanisms. One or more of these mechanisms may co-exist in a single bacterial isolate.

Cross-resistance

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

Interaction with other antibacterial agents

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

Susceptibility testing

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.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against pathogens listed under each indication that were susceptible to ceftaroline *in vitro*.

Complicated skin and soft tissue infections

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

Gram-negative organisms
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Morganella morganii*

Community-acquired pneumonia

Gram-positive organisms
- *Streptococcus pneumoniae*
- *Staphylococcus aureus* (methicillin-susceptible strains only)

Gram-negative organisms
- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*

Antibacterial activity against other relevant pathogens

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

Anaerobic Gram-positive organisms

Peptostreptococcus species

Anaerobic Gram-negative organisms

Fusobacterium species

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 4 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 5 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	402/431 (93.3)	397/422 (94.1)
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)

Organism	Ceftaroline N/N (%)	Vancomycin/Aztreonam n/N (%)
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	84/95 (88.4)	90/94 (95.7)
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 6 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 7 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 randomized, 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 randomized, 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 randomized, 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 randomized 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 8 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 9 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 (methicillin-susceptible strains only)	18/25 (72.0)	14/25 (56.0)
Gram-negative organism		
Haemophilus influenzae	15/18 (83.3)	17/20 (85.0)
Haemophilus parainfluenzae	16/16 (100.0)	15/17 (88.2)
Escherichia coli	10/12 (83.3)	9/12 (75.0)
Klebsiella pneumoniae	13/13 (100.0)	10/12 (83.3)

Asia CAP study

A total of 771 adults with a diagnosis of CAP were enrolled in a randomized, 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 hospitalized 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 10 and 11). 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 10 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 11 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 12 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 randomized, 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 randomized, 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 hospitalization 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 randomized 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 radiolabeled ceftaroline fosamil was 20.3 L, similar to the volume of extracellular fluid.

Metabolism

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

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

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 radiolabeled 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 adjustment 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.

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: Please refer to outer carton for details.

After reconstitution:

The reconstituted vial should be used immediately.

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, the diluted product must be used within 6 hours.

From a microbiological point of view, the medicinal product should be used immediately, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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 constituted solution 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 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 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.

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

Each vial is for single use only.

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

7. MANUFACTURER

ACS Dobfar S.p.A.
Viale Addetta, 2a/12 – 3/5,
20067 Tribiano,
Milano, Italy

Packager:
ACS Dobfar S.p.A.
Via A. Fleming 2
37135 Verona, Italy

Date of Revision: 06 JUN 2025

ZINFORO-0625