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 adults, adolescents and children over the age of 2 months.

4.2 Posology and method of administration
Dosage in adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg

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

Table 1 Dosage in adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg

Infection	Dosage	Frequency	Infusion time (minutes)	Recommended duration of antimicrobial treatment (days)
cSSTI	600 mg	every 12 hours	60	5-14
CAP	600 mg	every 12 hours	60	5-7

Dosage in children from 2 months to <12 years and adolescents aged from 12 to <18 years with bodyweight <33 kg

The recommended dosage of Zinforo is based on the age and weight of the child. Zinforo is administered every 8 hours by intravenous infusion over 60 minutes. The duration of treatment

should be guided by the type of infection to be treated, its severity, and the patient's clinical response.

The recommended durations of treatment by indication are the same as those shown in Table 1.

Table 2 Dosage in children aged from 2 months to <12 years and adolescents aged from 12 to <18 years with bodyweight < 33 kg

Age range cSSTI and CAP	**Dosage**	**Frequency**	**Infusion time (minutes)**
≥12 years to <18 years	12 mg/kg[a]	every 8 hours	60
≥2 years to <12 years	12 mg/kg[a]	every 8 hours	60
≥2 months to <2 years	8 mg/kg	every 8 hours	60

[a] The dose administered every 8 hours should not exceed 400 mg

The safety and efficacy in paediatric patients below the age of 2 months has not been established (see section 5.1).

Special populations

Patients with renal impairment
The dose should be adjusted when creatinine clearance (CrCL) is ≤50 ml/min. Dose recommendations for children and adolescents are based on PK modelling. Adolescents aged from 12 to <18 years with bodyweight ≥33 kg can receive either the dose regimen indicated in Table 3 or that in Table 4. End Stage Renal Disease (ESRD) patients can only be dosed as in Table 3.

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 children aged from 2 months to <2 years with moderate or severe renal impairment or ESRD.

Dosage in adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg with renal impairment

Adolescents aged from 12 to <18 years with bodyweight ≥33 kg can receive either the dose regimen indicated in Table 3 or that in Table 4.

Table 3 Dosage in adults and adolescents aged from 12 to <18 years with bodyweight ≥33 kg with renal impairment

Creatinine clearance[a] (ml/min)	Dosage regimen
>30 to ≤50	400 mg intravenously (over 60 minutes) every 12 hours
≥15 to ≤30	300 mg intravenously (over 60 minutes) every 12 hours
ESRD, including haemodialysis[b]	200 mg intravenously (over 60 minutes) every 12 hours

[a] calculated using the Cockcroft-Gault formula

[b] ceftaroline is haemodialyzable; thus Zinforo should be administered after haemodialysis on haemodialysis days

Dosage in children aged from 2 to <12 years and adolescents aged from 12 to <18 years with bodyweight <33 kg with renal impairment

Table 4 Dosage in children aged from 2 to <12 years and adolescents aged from 12 to <18 years with bodyweight <33 kg with renal impairment

Creatinine clearance[a] (ml/min)	Age	Dosage	Frequency	Infusion time (minutes)
> 30 to ≤50	≥12 years to <18 years	8 mg/kg[b]	Every 8 hours	60
	≥2 years to <12 years	8 mg/kg[b]	Every 8 hours	60
≥ 15 to ≤30	>12 years to <18 years	6 mg/kg[c]	Every 8 hours	60
	≥2 years to <12 years	6 mg/kg[c]	Every 8 hours	60

[a] calculated using the Schwartz formula

[b] The dose administered every 8 hours should not exceed 300 mg

[c] The dose administered every 8 hours should not exceed 200 mg

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. 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 special 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.

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), (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.

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 Zinforo (600 mg administered over 60 minutes every 12 hours).

The incidences of treatment emergent adverse events in the pooled Phase 3 cSSTI and CAP studies were similar in ceftaroline and comparator groups (45.7% vs. 46.7%, respectively). The most common adverse reactions occurring in ≥3% of patients treated with ceftaroline were diarrhoea, headache, nausea, 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 Zinforo (600 mg administered over 60 minutes every 12 hours) demonstrated that the safety profile of Zinforo

in these patients was similar to that observed in the pooled Phase 3 cSSTI and CAP studies.

A study (COVERS) was conducted of 506 adult patients with cSSTI treated with Zinforo (600 mg administered over 120 minutes every 8 hours). The most common adverse reactions occurring in ≥3% of patients treated with Zinforo were nausea, headache, and rash. The safety profile of Zinforo was similar to that observed in previous pooled Phase 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).

Paediatric population

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

The following adverse reactions have been identified during clinical trials with Zinforo. 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 normalized ratio increased
	Renal and urinary disorders	Blood creatinine increased
Rare (≥0.01% and <0.1%)	Blood and lymphatic system disorders	Eosinophilia
Not known	Blood and lymphatic system disorders	Agranulocytosis, neutropenia

Description of selected adverse reactions

Rash
Rash was observed at a common frequency in the pooled Phase III studies in cSSTI with administration of Zinforo every 12 hours (600 mg administered over 60 minutes every 12 hours) and the COVERS study in cSSTI with administration every 8 hours (600 mg administered over 120 minutes every 8 hours). However, the frequency of rash in the subgroup of Asian patients receiving Zinforo every 8 hours (COVERS) was very common (18.5%).

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

Ceftaroline can be 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 *Enterobacteriaceae* 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).

Susceptibility testing breakpoints
Ceftaroline susceptibility criteria are recommended based on pharmacokinetics and correlation of clinical and microbiological outcomes with zone diameter and minimum inhibitory concentrations (MIC) of the infecting organisms.
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptibility testing are presented below.

Organisms	Minimum Inhibitory Concentration (mg/l)	
	Susceptible (≤S)	Resistant (R>)
Staphylococcus aureus	1	1
Streptococcus pneumoniae	0.25	0.25
Streptococcus Groups A, B, C, G	Note[1]	Note[1]
Haemophilus influenzae	0.03	0.03
Enterobacteriaceae	0.5	0.5
Non-species related breakpoints[2]	0.5	0.5

Notes:
1. Infer susceptibility from susceptibility to benzylpenicillin.
2. Based on PK/PD target for Gram-negative organisms.

Susceptibility
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 the 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* group (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 resistance mechanisms.

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*

Clinical efficacy and safety
Complicated skin and soft tissue infections
A total of 1396 adults with documented complicated skin and soft tissue infections were enrolled in two identical randomised, multi-centre, multinational, double-blind studies (CANVAS 1 and CANVAS 2) comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to vancomycin plus aztreonam (1 g vancomycin administered intravenously over 60 minutes followed by 1 g aztreonam administered intravenously over 60 minutes every 12 hours). Patients with deep/extensive cellulites, 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

	Zinforo n/N (%)	Vancomycin/Aztreonam n/N (%)	Treatment difference (2-sided 95% CI)
CANVAS 1			
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6,2.1)
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2,6.2)
CANVAS 2			
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4,4.5)
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8,5.0)

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

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

Organism	Zinforo n/N (%)	Vancomycin/Aztreonam n/N (%)
Gram-positive organisms		
Staphylococcus aureus	352/378 (93.1)	336/356 (94.4)
MSSA (methicillin-susceptible)	212/228 (93.0)	225/238 (94.5)
MRSA (methicillin-resistant)	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*

Community-acquired pneumonia

A total of 1240 adults with a diagnosis of CAP were enrolled in two randomized, multi-centre, multinational, double-blind studies comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to ceftriaxone (1 g ceftriaxone administered intravenously over 30 minutes every 24 hours). The studies were identical except in one respect, in FOCUS 1 both treatment groups received 2 doses of oral clarithromycin (500 mg every 12 hours) as adjunctive therapy starting on Day 1. No adjunctive macrolide therapy was used in FOCUS 2. Patients with new or progressive pulmonary infiltrate(s) on chest radiography with clinical signs and symptoms consistent with CAP with the need for hospitalisation and intravenous therapy were enrolled in the studies. Treatment duration was 5 to 7 days. The modified intent-to-treat efficacy (MITTE) population included all patients who received any amount of study drug according to their 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

	Zinforo n/N (%)	Ceftriaxone n/N (%)	Treatment difference (2-sided 95% CI)
FOCUS 1			
CE	194/224 (86.6)	183/234 (78.2)	8.4(1.4,15.4)
MITTE	244/291 (83.8)	233/300 (77.7)	6.2 (-0.2,12.6)
FOCUS 2			
CE	193/235 (82.1)	166/215 (77.2)	4.9 (-2.5,12.5)
MITTE	235/289 (81.3)	206/273 (75.5)	5.9 (-1.0,12.7)

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

Table 9 Clinical cure rates by infecting pathogen from microbiologically evaluable patients with CAP (data from two integrated Phase 3 studies)

Organism	Zinforo n/N (%)	Ceftriaxone n/N (%)
Gram-positive organism		
Streptococcus pneumoniae	54/63 (85.7)	41/59 (69.5)
Staphylococcus aureus 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 randomized, multi-centre, double-blind study in Asia comparing Zinforo (600 mg administered intravenously over 60 minutes every 12 hours) to ceftriaxone (2 g administered intravenously over 30 minutes every 24 hours). Treatment duration was 5 to 7 days. The primary objective was to determine the non-inferiority in the clinical cure rate of ceftaroline treatment compared with that of ceftriaxone treatment at the TOC visit in the CE population of adult hospitalised patients with CAP (lower boundary of the 95% confidence interval for the difference in response rate [ceftaroline – ceftriaxone] greater than -10%).

The non-inferiority of ceftaroline 600 mg versus ceftriaxone 2 g was demonstrated in both the CE and MITT populations (Tables 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	Zinforo n/N (%)	Ceftriaxone n/N (%)
Gram-positive organism		
Streptococcus pneumoniae	19/22 (86.4)	13/15 (86.7)
Staphylococcus aureus (methicillin-susceptible strains only)	2/2 (100.0)	1/3 (33.3)
Gram-negative organism		
Haemophilus influenzae	9/10 (90.0)	6/7 (85.7)
Haemophilus parainfluenzae	0/0	4/6 (66.7)
Escherichia coli	3/3 (100.0)	5/6 (83.3)
Klebsiella pneumoniae	11/14 (78.6)	12/16 (75.0)

Paediatric studies

A study was conducted in paediatric patients aged 2 months to <18 years with cSSTI. The primary objective was to evaluate the safety and tolerability of ceftaroline versus vancomycin or cefazolin with or without aztreonam.

A study was conducted in paediatric patients aged 2 months to <18 years with CAP. The primary objective was to evaluate the safety and tolerability of ceftaroline versus ceftriaxone.

The studies demonstrated that ceftaroline is generally well tolerated in paediatric patients from 2 months to <18 years of age. Clinical cure rates at TOC were high and similar for both treatment groups in the MITT and CE populations.

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 administered over 60 minutes every 12 hours for up

to 14 days in healthy adults with normal renal function.

Distribution
The plasma protein binding of ceftaroline is low (approximately 20%) and 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 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 children 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 Zinforo, the pharmacokinetics of ceftaroline was similar between healthy elderly subjects (≥65 years of age), and healthy young adult subjects (18-45 years of age). There was a slight 33% increase in $AUC_{0-\infty}$ in the elderly that was mainly attributable to age-related changes in renal function. Zinforo dose adjustment is not required in elderly patients with creatinine clearance above 50 ml/min.

Paediatric patients
Dose adjustments are required for children aged from 2 months to <12 years and for adolescents aged 12 to <18 years with bodyweight <33 kg (see section 4.2). The safety and efficacy of Zinforo in children aged birth to <2 months have not been established.

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 24 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 24 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 constituted 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,
Operations Support Group, Ringaskiddy
County Cork, Ireland.

ZINF-SIN-1019/0
Date of Last Revision: October 2019