ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 adults and children from the age of 2 months (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

Posology

Adults and adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg: see Table 1.

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

Infection	Dosage	Frequency	Infusion time (minutes)	Duration of treatment (days)
cSSTI	600 mg	Every 12 hours	60	5-14
CAP	600 mg	Every 12 hours	60	5-7

Children aged from 2 months to < 12 years and adolescents aged from 12 to < 18 years with bodyweight < 33 kg: see Table 2. The recommended durations of treatment 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 and bodyweight	Dosage	Frequency	Infusion time (minutes)
≥ 12 years to < 18 years and bodyweight < 33 kg	12 mg/kg*	Every 8 hours	60
≥ 2 years to < 12 years	12 mg/kg*	Every 8 hours	60
≥ 2 months to < 2 years	8 mg/kg	Every 8 hours	60

* The dose administered every 8 hours should not exceed 400 mg

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 section 5.2). Dose recommendations for children and adolescents are based on 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 ESRD. 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.

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	Frequency	Infusion time (minutes)
> 30 to ≤ 50	400 mg	Every 12 hours	60
≥ 15 to ≤ 30	300 mg	Every 12 hours	60
End-stage renal disease (ESRD), including haemodialysis[b]	200 mg	Every 12 hours	60

[a] calculated using the Cockcroft-Gault formula
[b] Zinforo should be administered after haemodialysis on haemodialysis days

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 and bodyweight	Dosage[b]	Frequency	Infusion time (minutes)
> 30 to ≤ 50	≥ 12 years to < 18 years and bodyweight < 33 kg	8 mg/kg[c]	Every 8 hours	60
	≥ 2 years to < 12 years	8 mg/kg[c]	Every 8 hours	60
≥ 15 to ≤ 30	> 12 years to < 18 years and bodyweight < 33 kg	6 mg/kg[d]	Every 8 hours	60
	≥ 2 years to < 12 years	6 mg/kg[d]	Every 8 hours	60

[a] calculated using the Schwartz formula
[b] dose is based on CrCL. CrCL should be closely monitored and the dose adjusted according to changing renal function
[c] The dose administered every 8 hours should not exceed 300 mg
[d] The dose administered every 8 hours should not exceed 200 mg

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

Paediatric population
The safety and efficacy of Zinforo in children below the age of 2 months have not yet been established.

Method of administration
Zinforo is administered by intravenous infusion over 60 minutes for all infusion volumes (50 ml, 100 ml or 250 ml) (see section 6.6).

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 the 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
Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftaroline fosamil. Zinforo is contraindicated in patients with a history of hypersensitivity to cephalosporins. In addition, it is contraindicated in patients with a history of an immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (see section 4.3). Zinforo should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or carbapenems. If a severe allergic reaction occurs during treament with Zinforo, the medicinal product should be discontinued and appropriate measures taken.

Clostridium difficile-associated diarrhoea
Antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftaroline fosamil and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftaroline fosamil (see section 4.8). In such circumstance, the discontinuation of therapy with ceftaroline fosamil and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered.

Non-susceptible organisms
Superinfections may occur during or following treatment with Zinforo.

Patients with pre-existing seizure disorder
Seizures have occurred in toxicology studies at 7-25 times human ceftaroline C_{max} levels (see section 5.3). Clinical study experience with ceftaroline fosamil in patients with pre-existing seizure disorders is very limited. Therefore, Zinforo should be used with caution in this patient population.

Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia
The development of a positive direct antiglobulin test (DAGT) may occur during treatment with cephalosporins. The incidence of DAGT seroconversion in patients receiving ceftaroline fosamil was 10.7% in the four pooled pivotal 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). In clinical studies there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. However, the possibility that haemolytic anaemia may occur in association with cephalosporins including Zinforo treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zinforo should be investigated for this possibility.

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

There is no experience with ceftaroline in the treatment of cSSTI in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

The interaction potential of ceftaroline or ceftaroline fosamil on medicinal products metabolised by CYP450 enzymes is expected to be low since they are not inhibitors nor inducers of CYP450 enzymes *in vitro*. Ceftaroline or ceftaroline fosamil are not metabolised by CYP450 enzymes *in vitro*, therefore co-administered CYP450 inducers or inhibitors are unlikely to influence the pharmacokinetics of ceftaroline.

Ceftaroline is neither a substrate, nor an inhibitor of renal uptake transporters (OCT2, OAT1, and OAT3) *in vitro*. Therefore, interactions of ceftaroline with medicinal products that are substrates or inhibitors (e.g. probenecid) of these transporters would not be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of ceftaroline fosamil in pregnant women. Animal studies conducted in rat and rabbit do not indicate harmful effects with respect to reproductive toxicity at exposures similar to therapeutic concentrations. Following administration throughout pregnancy and lactation in the rat, there was no effect on pup birth weight or growth, although minor changes in foetal weight and delayed ossification of the interparietal bone were observed when ceftaroline fosamil was administered during organogenesis (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Zinforo during pregnancy unless the clinical condition of the woman requires treatment with an antibiotic with Zinforo's antibacterial profile.

Breast-feeding
It is unknown whether ceftaroline fosamil or ceftaroline is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zinforo therapy taking into account the benefit of therapy for the woman.

Fertility
The effects of ceftaroline fosamil on fertility on humans have not been studied. Animal studies with ceftaroline fosamil do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Dizziness may occur and this may have an effect on driving and use of machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Pooled Phase III studies
In four pivotal clinical trials, 1305 adult patients were treated with Zinforo (600 mg administered over 60 minutes every 12 hours).

The most common adverse reactions occurring in ≥ 3% of patients treated with Zinforo were diarrhoea, headache, nausea, and pruritus, and were generally mild or moderate in severity.

Additional Phase III studies
A study 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 of 506 adult patients with cSSTI was conducted 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).

Tabulated list of adverse reactions
The following adverse reactions have been identified during clinical trials and post-marketing experience with Zinforo. Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are derived according to the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), not known (cannot be estimated from the available data).

Table 5 Frequency of adverse reactions by system organ class from clinical trials and post-marketing experience

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations			*Clostridium difficile* colitis (see section 4.4)		

System organ class	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			Anaemia, leucopenia, neutropenia, thrombocytopenia, prothrombin time (PT) prolonged, activated partial thromboplastin time (aPTT) prolonged, international normalized ratio (INR) increased	Agranulocytosis	Eosinophilia
Immune system disorders		Rash, pruritus	Anaphylaxis (see sections 4.3 and 4.4), hypersensitivity (e.g. urticaria, lip and face swelling) (see sections 4.3 and 4.4)		
Nervous system disorders		Headache, dizziness			
Vascular disorders		Phlebitis			
Gastrointestinal disorders		Diarrhoea, nausea, vomiting, abdominal pain			
Hepatobiliary disorders		Increased transaminases			
Renal and urinary disorders			Blood creatinine increased		
General disorders and administration site conditions		Pyrexia, infusion site reactions (erythema, phlebitis, pain)			
Investigations	Coombs Direct Test Positive (see section 4.4)				

Description of selected adverse reactions

Rash
Rash was observed at a common frequency in both 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 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 was very common (18.5%).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited data in patients receiving higher than recommended Zinforo dosages show similar adverse reactions as observed in the patients receiving recommended dosages. Relative overdosing could occur in patients with moderate renal impairment. Treatment of overdose should follow standard medical practice.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The active moiety after Zinforo administration is ceftaroline.

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

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. Organisms that express these enzymes and which are therefore resistant to ceftaroline occur at very variable rates between countries and between healthcare facilities within countries. If ceftaroline is commenced before susceptibility test results are available then local information on the risk of encountering organisms that express these enzymes should be taken into consideration. Resistance may also be mediated by bacterial

impermeability or drug efflux pump mechanisms. One or more of these mechanisms may co-exist in a single bacterial isolate.

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

Susceptibility testing breakpoints

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

Organisms	**MIC breakpoints (mg/L)**	
	Susceptible (≤ S)	**Resistant (R>)**
Staphylococcus aureus	1	1
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.

PK/PD 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 be the parameter that best correlates with the efficacy of ceftaroline.

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

Complicated skin and soft tissue infections
Gram-positive micro-organisms
- *Staphylococcus aureus* (including methicillin-resistant strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)
- *Streptococcus dysgalactiae*

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

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

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

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

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

Anaerobic micro-organisms
Gram-positive micro-organisms
- *Peptostreptococcus* spp.

Gram-negative micro-organisms
- *Fusobacterium* spp.

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

Information from clinical studies
Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Zinforo in the paediatric population aged birth to < 2 months (see section 4.2 for information on paediatric use).

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 radiolabelled ceftaroline fosamil was 20.3 l, similar to the volume of extracellular fluid.

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

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

Elimination
Ceftaroline is primarily eliminated by the kidneys. Renal clearance of ceftaroline is approximately equal, or slightly lower than the glomerular filtration rate in the kidney, and *in vitro* transporter studies indicate that active secretion does not contribute to the renal elimination of ceftaroline.

The mean terminal elimination half-life of ceftaroline in healthy adults is approximately 2.5 hours.

Following the administration of a single 600 mg intravenous dose of radiolabelled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in faeces.

Special populations
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.

Hepatic impairment
The pharmacokinetics of ceftaroline in patients with hepatic impairment has not been established. As ceftaroline does not appear to undergo significant hepatic metabolism, the systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment. Therefore, no dosage adjustment is recommended for patients with hepatic impairment.

Elderly
Following administration of a single 600 mg intravenous dose of ceftaroline fosamil, the pharmacokinetics of ceftaroline were similar between healthy elderly subjects (≥ 65 years of age), and healthy young adult subjects (18-45 years of age). There was a 33% increase in $AUC_{0-\infty}$ in the elderly that was mainly attributable to age-related changes in renal function. Zinforo dose adjustment is not required in elderly patients with creatinine clearance above 50 ml/min.

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

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

5.3 Preclinical safety data

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

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

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

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

Juvenile toxicity
Intravenous bolus dosing of ceftaroline fosamil to suckling rats from post-natal day 7 to 20 was well tolerated at plasma exposures approximately 2-fold higher than those for paediatric patients. Renal cortical cysts were oberved in all groups, including controls, on PND50. The cysts involved a small portion of the kidney and ocurred in the absence of significant changes in either renal function or urinary parameters. Therefore, these findings were not considered to be adverse.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine

6.2 Incompatibilities

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

6.3 Shelf life

Dry powder: 3 years

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 24 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. 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 8ºC, 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 either 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) or Lactated Ringer's solution. A 250 ml, 100 ml or 50 ml infusion bag can be used to prepare the infusion, based on the patient's volume requirements. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

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. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/785/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Facta Farmaceutici S.p.A.
Nucleo Industriale S. Atto
64100 Teramo
Italy

AstraZeneca AB
Gärtunavägen, B674:5
SE-151 85 Södertälje
Sweden

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/ risk profile or as a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zinforo 600 mg powder for concentrate for solution for infusion
ceftaroline fosamil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Arginine

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package in order to protect from light.
Read the leaflet for the shelf life of the reconstituted product.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/785/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zinforo 600 mg powder for concentrate for solution for infusion
ceftaroline fosamil
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zinforo 600 mg powder for concentrate for solution for infusion
Ceftaroline fosamil

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zinforo is and what it is used for

What Zinforo is
Zinforo is an antibiotic medicine that contains the active substance ceftaroline fosamil. It belongs to a group of medicines called 'cephalosporin antibiotics.'

What Zinforo is used for
Zinforo is used to treat children from the age of 2 months and adults with:
- infections of the skin and the tissues below the skin
- an infection of the lungs called 'pneumonia'

How Zinforo works
Zinforo works by killing certain bacteria, which can cause serious infections.

2. What you need to know before you use Zinforo

Do not use Zinforo if:
- you are allergic to ceftaroline fosamil or any of the other ingredients of Zinforo (listed in section 6)
- you are allergic to other cephalosporin antibiotics
- you have had previous severe allergic reactions to other antibiotics like penicillin or carbapenem.

Do not use Zinforo if any of the above applies to you. If you are not sure, talk to your doctor or nurse before using Zinforo.

Warnings and precautions
Talk to your doctor or nurse before using your medicine if:
- you have kidney problems (your doctor may have to prescribe a lower dose)
- you have ever had fits (seizures or convulsions)

- you have ever had any non-severe allergic reactions to other antibiotics like penicillin or carbapenem
- you have had severe diarrhoea whilst taking antibiotics in the past

You may get another infection caused by another bacteria during or following treatment with Zinforo.

Lab Test
You may develop an abnormal lab test (called Coombs test) that looks for certain antibodies which may act against your red blood cells.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before using Zinforo.

Children and adolescents
Zinforo should not be used in children below the age of 2 months as not enough data exist in these populations.

Other medicines and Zinforo
Tell your doctor or nurse if you are using, have recently used or might use any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy and breast-feeding
Tell your doctor before using Zinforo if you are pregnant. Do not use this medicine during pregnancy unless your doctor has told you to.

Tell your doctor before using Zinforo if you are breast-feeding or are planning to breast-feed. Your doctor may ask you to stop breast-feeding during treatment with Zinforo.

Ask your doctor for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Zinforo may cause side effects such as dizziness. This may impair your ability to drive or operate machinery

3. How to use Zinforo

Zinforo will be given to you by a doctor or nurse.

How much to use
The usual dose for adults is 600 mg every 12 hours. The usual dose for children depends on the age and weight of the child and is given every 8 or 12 hours. It is given as a drip into a vein lasting 60 minutes.

A course of treatment usually lasts for 5 to 14 days for skin infections and 5 to 7 days for pneumonia.

Patients with kidney problems
If you have kidney problems your doctor may lower your dose because Zinforo is removed from your body by the kidneys.

If you use more Zinforo than you should
If you think you have been given too much Zinforo, tell your doctor or nurse straight away.

If you miss a dose of Zinforo
If you think you have missed a dose, tell your doctor or nurse straight away.

If you have any further questions on the use of this product, ask your doctor or nurse.

4. Possible side effects

Like all medicines, Zinforo can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Tell your doctor straight away if you get these symptoms as you may need urgent medical treatment:

- Sudden swelling of your lips, face, throat or tongue; a severe rash; and, swallowing or breathing problems. These may be signs of a severe allergic reaction (anaphylaxis) and may be life-threatening
- Diarrhoea that becomes severe or does not go away or stool that contains blood or mucus during or after treatment with Zinforo. In this situation, you should not take medicines that stop or slow bowel movement.

Very common (affects more than 1 in 10 patients)

- Changes in a blood test called a 'Coombs test' commonly seen in patients receiving this type of antibiotic. This test looks for certain antibodies which may act against your red blood cells.

Common (affects less than 1 in 10 patients)

- Fever
- Headache
- Feeling dizzy
- Itching, skin rash
- Diarrhoea, stomach pain
- Feeling sick (nausea) or being sick (vomiting)
- More enzymes produced by your liver (as shown in blood tests)
- Pain and irritation of the veins
- Redness, pain or swelling where the injection was given.

Uncommon (affects less than 1 in 100 patients)

- Anaemia
- Raised itchy rash (hives)
- An increase in the level of creatinine in your blood. Creatinine shows how well your kidneys are working.
- Bleeding or bruising more than usual. This may be because the level of platelets in your blood has dropped.
- Changes in tests which measure how well your blood clots.
- A decrease in the total number of and of certain white blood cells in your blood (leucopenia and neutropenia).

Rare (affects less than 1 in 1,000 patients)

- A significant decrease in the number of certain white blood cells in your blood (agranulocytosis). You may experience fever, flu-like symptoms, sore throat, or any other infection which may be serious.

Frequency not known (cannot be estimated from available data)

- An increase in the number of certain white blood cells in your blood (eosinophilia).

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zinforo

Keep out of the sight and reach of children.

Do not use Zinforo after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Store below 30°C.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zinforo contains
- Each vial contains 600 mg of ceftaroline fosamil.
- The other ingredient is arginine.

What Zinforo looks like and contents of the pack
Zinforo is a pale yellowish-white to light yellow powder for concentrate for solution for infusion in a vial. It is available in packs containing 10 vials.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics before prescribing.

Aseptic technique must be followed in preparing the infusion solution. The contents of Zinforo vial should be reconstituted with 20 ml of sterile water for injections. Instructions for the reconstitution of Zinforo vial are summarized below:

Dosage strength (mg)	Volume of diluent to be added (ml)	Approximate ceftaroline concentration (mg/ml)	Amount to be withdrawn
600	20	30	Total volume

The reconstituted solution must be further diluted to produce Zinforo solution for infusion. A 250 ml, 100 ml or 50 ml infusion bag can be used to prepare the infusion, based on the patient's volume requirements. Appropriate infusion diluents include: 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) or Lactated Ringer's solution. The resulting solution should be administered over 60 minutes for all infusion volumes (50 ml, 100 ml or 250 ml).

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.

Reconstitution time is less than 2 minutes. Mix gently to reconstitute and check to see that the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration.

The colour of Zinforo infusion solutions ranges from clear, light to dark yellow depending on the concentration and storage conditions. It is free of any particles. When stored as recommended, the product potency is not affected.

Studies have shown that Zinforo solutions for infusion are stable for up to 6 hours at room temperature. Alternatively they are stable for up to 24 hours under refrigerated storage. 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.

The compatibility of Zinforo with other medicines has not been established. Zinforo should not be mixed with or physically added to solutions containing other drugs.

Each vial is for single use only.

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