Zinforo 600 mg powder for concentrate for solution for infusion

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 "List of excipients".

Pharmaceutical form

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

Therapeutic indications

Zinforo is indicated in adults for the treatment of the following infections (see sections "Special warnings and precautions for use" and "Pharmacodynamic properties"):

- 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.

Posology and method of administration

Posology

For the treatment of cSSTI and CAP, the recommended dose is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older. The recommended treatment duration for cSSTI is 5 to 14 days and the recommended duration of treatment for CAP is 5 to 7 days.

Special populations

Elderly patients (≥ 65 years)

No dosage adjustment is required for the elderly with creatinine clearance values > 50 ml/min (see section "Pharmacokinetic properties").

Renal impairment

The dose should be adjusted when creatinine clearance (CrCL) is ≤ 50 ml/min, as shown below (see sections "Special warnings and precautions for use" and "Pharmacokinetic properties").

Creatinine clearance (ml/min)	Dosage regimen	Frequency
> 30 to ≤ 50	400 mg intravenously (over 60 minutes)	every 12 hours

There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis (see section "Special warnings and precautions for use").

Hepatic impairment

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

Paediatric population

The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established. No data are available (see section "Pharmacokinetic properties").

Method of administration

Zinforo is administered by intravenous infusion over 60 minutes (see section "Instructions for use and handling").

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section "List of 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).

Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions are possible (see sections "Contraindications" and "Undesirable effects").

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 "Contraindications"). 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 "Undesirable effects"). 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 "Pre clinincal safety data"). 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.

Renal impairment

There is insufficient data to make specific dosage adjustment recommendations for patients with severe renal impairment (CrCL ≤ 30 ml/min) and end-stage renal disease (ESRD), including patients undergoing haemodialysis. Therefore, use of Zinforo is not recommended in these patient populations (see section "Pharmacokinetic properties").

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 pooled pivotal studies. 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.

Interactions 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 P450 enzymes is expected to be low since they are not inhibitors nor inducers of P450 enzymes *in vitro*. Ceftaroline or ceftaroline fosamil are not metabolised by P450 enzymes *in vitro*, therefore co-administered P450 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.

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 "Pre clinincal safety data).

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 "Pre clinincal safety data").

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 "Undesirable effects").

Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

The following adverse reactions have been identified during clinical trials 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).

Table 1 Frequency of adverse reactions by system organ class

System organ class	Very common	Common	Uncommon
Infections and infestations			*Clostridium difficile* colitis (see section "Special warnings and precautions for use")
Blood and lymphatic system disorders			Anaemia, leucopoenia, thrombocytopenia, prothrombin time (PT) prolonged, activated partial thromboplastin time (aPTT) prolonged, international normalized ratio (INR) increased
Immune system disorders		Rash, pruritus	Anaphylaxis (see sections "Contraindications" and "Special warnings and precautions for use"), hypersensitivity (e.g. urticaria, lip and face swelling) (see sections "Contraindications" and "Special warnings and precautions for use")
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 "Special warnings and precautions for use")		

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; 21.6% of the dose was removed over a 4 hour dialysis period.

Pharmacodynamic properties

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

The active moiety after Zinforo administration is ceftaroline.

Mode 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).

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*

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.

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 P450 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 radiolabeled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in faeces.

Special populations

Renal impairment

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

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 patients (≥ 65 years)
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
The safety and efficacy of Zinforo in children aged birth to < 18 years have not yet been established.

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

Pre clinincal 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.

List of excipients
Arginine

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section "Instructions for use and handling".

Shelf life
Please refer to expiry date on the outer carton.

After reconstitution:
The reconstituted vial should be used immediately.

After dilution:
Once the intravenous solution is prepared with diluents listed in section "Instructions for use and handling" 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 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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 "Shelf life".

Pack size
Please refer to outer carton for pack size.

Instructions for use and 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. Routinely, a 250 ml infusion bag should be used to prepare the infusion and only in exceptional patients for whom there could be great concern over volumes infused should a 50 ml or 100 ml infusion bag be used. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Each vial is for single use only.

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

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Name and address of manufacturer
Manufactured by ACS Dobfar S.p.A., Milan, Italy and Facta Farmaceutici S.p.A., Teramo, Italy for AstraZeneca AB, Södertälje, Sweden.