PT PFIZER INDONESIA
Local Product Document

Generic Name: Ceftaroline fosamil
Trade Name: ZINFORO™
CDS Effective Date: February 08, 2022
Supersedes: August 11, 2016

Qualitative and quantitative composition
Each vial contains ceftaroline fosamil acetic acid solvate monohydrate equivalent to 600 mg ceftaroline fosamil that equivalent to 530 mg ceftaroline.

For excipients, see section *List of excipients*.

Pharmaceutical form
Powder for concentrate for solution for infusion

A pale yellowish-white to light yellow powder

Therapeutic indication
ZINFORO™ is indicated for the treatment of adult (≥18 years of age) patients with complicated skin and soft tissue infections (cSSTI) caused by susceptible isolates of the designated microorganism: *Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumonia* and *Klebsiella oxytoca*.

Usage:
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftaroline and other antibacterial drugs, ceftaroline should be used to treat only cSSTI that are proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Posology and method of administration
The recommended dosage of ZINFORO™ is 600 mg administered every 12 hours by intravenous infusion over 5 to 60 minutes (standard dose) in patients ≥18 years of age for duration of 5-14 days. The duration (see Table 1) of treatment should be guided by the severity of infection and the patient's clinical response.

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

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

Table 1 Dosage in patients with normal renal function (Creatine Clearance (CrCL) >50 mL/min):

Indications/Recommended duration of treatment (days)	Posology	Infusion time (minutes)[a]/Frequency
cSSTI[b] / 5 – 14	600 mg	5 – 60/every 12 hours
cSSTI[b] confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[c]/5 – 14	600 mg	120/every 8 hours

[a] The 5 minute infusion time is based on pharmacokinetic and pharmacodynamic analyses.
[b] Complicated skin and soft tissue infections (cSSTI) indication.
[c] Based on pharmacokinetic and pharmacodynamic analyses. See sections *Special warnings and special precautions for use* and *Pharmacodynamic properties*.

Special populations

Patients with renal impairment

The dose should be adjusted when creatinine clearance (CrCL) is ≤50 mL/min as shown in Table 2.

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

Indications/Recommended duration of treatment (days)	Creatinine clearance (mL/min)[a]	Posology	Infusion time (minutes)[b]/Frequency
cSSTI[c] / 5 – 14	>30 to ≤50	400 mg	5 – 60/every 12 hours
	≥15 to ≤30	300 mg	
	ESRD, including haemodialysis[e]	200 mg	
cSSTI[c] confirmed or suspected to be caused by *S. aureus* with an MIC = 2 mg/L or 4 mg/L to ceftaroline[d]/5 – 14	>30 to ≤50	400 mg	120/every 8 hours
	≥15 to ≤30	300 mg	
	ESRD, including haemodialysis[f]	200 mg	

[a] Calculated using the Cockcroft-Gault formula for adults. Dose is based on CrCL. CrCL should be closely monitored and the dose adjusted according to changing renal function.
[b] The 5 minute infusion time is based on pharmacokinetic and pharmacodynamic analyses.
[c] Complicated skin and soft tissue infections (cSSTI) indication.
[d] Based on pharmacokinetic and pharmacodynamic analyses. See sections *Special warnings and special precautions for use* and *Pharmacodynamic properties*.
[e] Ceftaroline is haemodialyzable; thus ZINFORO™ should be administered after haemodialysis on haemodialysis days.

Patients with hepatic impairment

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

Elderly patients

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

Paediatric patients

Safety and efficacy in paediatric patients have not been established (see section *Pharmacokinetic properties*).

Constitution and compatibility

See section *Instructions for use, handling and disposal*.

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).

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 *Contraindications* and *Undesirable effects*).

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 *Contraindications*).

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 *Undesirable effects*). 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 *Preclinical safety data*). Clinical study experience with ceftaroline in patients with pre-existing seizure disorders is limited. Therefore, ZINFORO™ should be used with caution in this patient population.

Direct antiglobulin test (Coombs test) seroconversion

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with cephalosporins. The incidence of DAGT seroconversion in patients receiving ceftaroline fosamil was 11.2% in the five pooled Phase 3 studies with administration every 12 hours (600 mg administered over 60 minutes every 12 hours) and 32.3% in a study in patients receiving ceftaroline fosamil every 8 hours (600 mg administered over 120 minutes every 8 hours). There was no evidence of haemolysis in any patient receiving ceftaroline fosamil who developed a positive DAGT.

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

There are limited clinical data for ceftaroline in treating cSSTI in adults caused by *S. aureus* with an MIC >1 mg/L to ceftaroline and there are no clinical data for treating *S. aureus* with an MIC = 2 mg/L to 4 mg/L to ceftaroline. Therefore, the recommended dosages of ZINFORO™ to treat cSSTI caused by *S. aureus* with an MIC >1 mg/L to ceftaroline are based on pharmacokinetic/pharmacodynamic modelling and simulation (see section *Posology and method of administration*). Zinforo should not be used to treat cSSTI due to *S. aureus* for which the ceftaroline MIC is > 4 mg/L.

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

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 CYP450 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 CYP450 enzymes *in vitro*. Ceftaroline is not metabolised by CYP450 enzymes *in vitro*, so co-administered CYP450 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.

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 *Preclinical safety data*). 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.

Effects on ability to drive and to use machines
Undesirable effects e.g. dizziness may occur and this may have an effect on the ability to drive and use of machines (see section *Undesirable effects*).

Undesirable effects

Pooled Phase III studies
The incidences of treatment emergent adverse events were similar in ceftaroline and comparator groups (45.7% versus 46.7%, respectively). The most common adverse reactions occurring in ≥3% of patients treated with ceftaroline were diarrhoea, headache, nausea, and pruritus, and were generally mild or moderate in severity.

Additional Phase III studies
A study (COVERS) was conducted of 506 adult patients with cSSTI treated with ceftaroline fosamil (600 mg administered over 120 minutes every 8 hours). The most common adverse reactions occurring in ≥3% of patients treated with ceftaroline fosamil were nausea, headache, and rash. The safety profile of ceftaroline fosamil 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 *Special warnings and special precautions for use*).

The following adverse reactions have been identified during clinical trials with ceftaroline fosamil.

Table 3 ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

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

*Adverse Drug Reaction (ADR) identified post marketing.

Description of selected adverse reactions

Rash

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

Overdose

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

Patients with renal impairment

Relative overdosing could occur in patients with moderate to severe renal impairment. Neurological sequelae, including encephalopathy, have been noted in cases where beta-lactam antibiotics (including cephalosporins) have been given to patients with impaired renal function without reducing the dose (see section *Posology and method of administration*).

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

Pharmacological properties

Pharmacodynamic properties

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 high affinity for the altered PBPs found in these organisms.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactam antimicrobial agents, the percent time above the minimum inhibitory concentration (MIC) of the infecting organism over the dosing interval (%T >MIC) has been shown to best correlate with the antimicrobial activities for ceftaroline.

Mechanisms of resistance

Ceftaroline is not active against strains of *Enterobacterales* producing extended-spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases or class C (AmpC cephalosporinases). Resistance may also be mediated by bacterial impermeability or drug efflux pump mechanisms. One or more of these mechanisms may co-exist in the same bacterium.

Cross-resistance

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

Interaction with other antibacterial agents

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

Susceptibility testing

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is questionable.

The susceptibility to ceftaroline of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

Clinical efficacy against specific pathogens
Efficacy has been demonstrated in clinical studies against pathogens 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*

Gram-negative organisms

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*

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

Anaerobic Gram-positive organisms
Peptostreptococcus species

Anaerobic Gram-negative organisms
Fusobacterium species

Clinical efficacy and safety
Complicated skin and soft tissue infections
A total of 1396 adults with documented complicated skin and soft tissue infections were enrolled in two identical randomised, multi-centre, multinational, double-blind studies (CANVAS 1 and CANVAS 2) comparing ceftaroline fosamil (600 mg administered intravenously over 60 minutes every 12 hours) to vancomycin plus aztreonam (1 g vancomycin administered intravenously over 60 minutes followed by 1 g aztreonam administered intravenously over 60 minutes every 12 hours). Patients with deep/extensive cellulitis, a major abscess, a wound infection (surgical or traumatic), infected bites, burns or ulcers, or any lower extremity infection in patients with either pre-existing diabetes mellitus or peripheral vascular disease, were eligible for the studies. Treatment duration was 5 to 21 days. The modified intent-to-treat (MITT) population included all patients who received any amount of study drug according to their randomised treatment group. The clinically evaluable (CE) population included patients in the MITT population with sufficient adherence to the protocol.

The primary efficacy endpoint was the clinical response at the Test of Cure (TOC) visit in the co-primary populations of the CE and MITT patients in the table below.

Table 4 Clinical cure rates at TOC from two Phase 3 studies in cSSTI after 5 to 21 days of therapy

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

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

Table 5 Clinical cure rates by infecting pathogen from microbiologically evaluable patients with cSSTI (data from two integrated Phase 3 studies)

Organism	Ceftaroline Fosamil N/N (%)	Vancomycin/Aztreonam n/N (%)
Gram-positive organisms		
Staphylococcus aureus	352/378 (93.1)	336/356 (94.4)
MSSA (methicillin-susceptible strains)	212/228 (93.0)	225/238 (94.5)
MRSA (methicillin-resistant strains)	142/152 (93.4)	115/122 (94.3)
Streptococcus pyogenes	56/56 (100.0)	56/58 (96.6)
Streptococcus agalactiae	21/22 (95.5)	18/18 (100.0)
Streptococcus dysgalactiae	13/13 (100.0)	15/16 (93.8)
Streptococcus anginosus group[a]	12/13 (92.3)	15/16 (93.8)
Gram-negative organisms		
Escherichia coli	20/21 (95.2)	19/21 (90.5)
Klebsiella pneumoniae	17/18 (94.4)	13/14 (92.9)
Morganella morganii	11/12 (91.7)	5/6 (83.3)
Klebsiella oxytoca	10/12 (83.3)	6/6 (100.0)

[a] Includes *S. anginosus, S. intermedius,* and *S. constellatus*

Pharmacokinetic properties

The C_{max} and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to 1000 mg. No appreciable accumulation of ceftaroline is observed following multiple intravenous infusions of 600 mg every 8 or 12 hours in healthy adults with normal renal function.

The systemic exposure (AUC), $T_{1/2}$, and clearance of ceftaroline were similar following administration of 600 mg ceftaroline fosamil in a volume of 50 mL to healthy adult subjects every 8 hours for 5 days as 5 minute or 60 minute infusions, and the T_{max} of ceftaroline occurred about 5 minutes after the end of the ceftaroline fosamil infusion for both infusion durations. The mean (SD) C_{max} of ceftaroline was 32.5 (4.82) mg/L for the 5 minute infusion duration (n=11) and 17.4 (3.87) mg/L for the 60 minute infusion duration (n=12).

Distribution

The plasma protein binding of ceftaroline is low (approximately 20%) and ceftaroline is not distributed into erythrocytes. The median steady-state volume of distribution of ceftaroline in healthy adult males following a single 600 mg intravenous dose of radiolabeled ceftaroline fosamil was 20.3 L, similar to the volume of extracellular fluid.

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

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

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

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

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

Special populations
Patients with renal impairment
Dosage adjustments are required in adults with CrCL ≤50 mL/min (see section *Posology and method of administration*).

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

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

Paediatric patients
The safety and efficacy of ceftaroline fosamil in paediatric patients have not been established.

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

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, or other patients. No dosage adjustment is recommended based on race.

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.

List of excipients

L-arginine

Incompatibilities

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

Shelf life

Dry powder: 3 years

After constitution:

The constituted vial should be used immediately (within 30 minutes).

After dilution:

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

From a microbiological point of view, the medicinal product should be used immediately unless constitution 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.

Special precautions for storage

Store below 30°C

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

For storage conditions of the constituted and diluted medicinal product, see section *Shelf life.*

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.

Instructions for use, handling and disposal

The powder must be constituted with water for injections and the resulting constituted solution must then be immediately diluted prior to use. The constituted 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 sterile water for injections. The resulting constituted solution should be shaken prior to being transferred to an infusion bag or bottle containing one of the following diluents:

- sodium chloride 9 mg/mL (0.9%) solution for injection
- dextrose 50 mg/mL (5%) solution for injection
- sodium chloride 4.5 mg/mL and dextrose 25 mg/mL solution for injection (0.45% sodium chloride and 2.5% dextrose)
- Lactated Ringer's solution

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 constitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

One mL of the constituted solution contains 30 mg of ceftaroline fosamil.

For storage conditions of the constituted and diluted medicinal product, see section *Shelf life*.

Each vial is for single use only.

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

Supply

Box of 10 vials @ 600 mg (Reg. No.: DKI1843900280A1)

HARUS DENGAN RESEP DOKTER

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