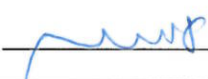


שם התכשיר: ZINFORO מספר הרישום: 150-76-33887
 אני הרוקחת הממונה עידית שלם אבידר של בעל הרישום: Pfizer PFE Pharmaceuticals
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 בתאריך 09.2019 ועודכן ע"י החברה בתאריך מאי 2020 ובתאריך יולי 2020.
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 Pfizer PFE Pharmaceuticals
 Israel Ltd.
 Idit Shallem-Avidar
 License No. 5540
 תאריך: 9/7/20 חתימה: 

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 in adults and children from age of 2 months for the treatment of the following infections (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

The recommended durations of treatment are 5-14 days for cSSTI and 5-7 days for CAP.

Table 1 Dosage in adults with normal renal function, creatinine clearance (CrCL) > 50 mL/min

Indications	Posology (mg/infusion)	Infusion time (minutes)/Frequency
Complicated skin and soft tissue infections (cSSTI) Community-acquired pneumonia (CAP)	600 mg	60/every 12 hours

Table 2 Dosage in paediatric patients with normal renal function, creatinine clearance (CrCL) > 50 mL/min*

Indications	Age group	Posology (mg/infusion)	Infusion time (minutes)/Frequency
Complicated skin and soft tissue infections (cSSTI) Community-acquired pneumonia (CAP)	Adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	600 mg	60/every 12 hours
	Adolescents aged from 12 years to < 18 years bodyweight < 33 kg and children ≥ 2 years to < 12 years	12 mg/kg to a maximum of 400 mg	60/every 8 hours
	Infants ≥ 2 months to < 2 years	8 mg/kg	60/every 8 hours

^a* Calculated using the Schwartz formula (in mL/min/1.73 m²) for paediatric patients.

Special populations

Elderly patients (≥ 65 years)

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). The recommended durations of treatment are 5-14 days for cSSTI and 5-7 days for CAP.

Table 3 Dosage in adults with impaired renal function, creatinine clearance (CrCL) ≤ 50 mL/min

Indications	Creatinine clearance (mL/min) ^a	Posology (mg/infusion)	Infusion time (minutes)/Frequency
<u>Standard dose</u>	> 30 to ≤ 50	400 mg	60/every 12 hours
Complicated skin and soft tissue infections(cSSTI)	≥ 15 to ≤ 30	300 mg	

Indications	Creatinine clearance (mL/min) ^a	Posology (mg/infusion)	Infusion time (minutes)/Frequency
Community-acquired pneumonia (CAP)	ESRD, including haemodialysis ^b	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 Ceftaroline is haemodialyzable; thus Zinforo should be administered after haemodialysis on haemodialysis days.

Dose recommendations for children and adolescents are based on pharmacokinetic (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 End-stage renal disease (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 4 Dosage in paediatric patients with impaired renal function, creatinine clearance (CrCL) ≤ 50 mL/min

Indications	Age group	Creatinine clearance (mL/min) ^a	Posology (mg/infusion)	Infusion time (minutes)/Frequency
Standard dose	Adolescents aged from 12 to < 18 years with bodyweight ≥ 33 kg	> 30 to ≤ 50	400 mg	60/every 12 hours
		≥ 15 to ≤ 30	300 mg	
		ESRD, including haemodialysis ^b	200 mg	
Complicated skin and soft tissue infections (cSSTI)	Adolescents aged from 12 years to < 18 years bodyweight < 33 kg	> 30 to ≤ 50	8 mg/kg to a maximum of 300 mg	60/every 8 hours
		≥ 15 to ≤ 30	6 mg/kg to a maximum of 200 mg	
Community-acquired pneumonia (CAP)	and children ≥ 2 years to < 12 years			

^a Calculated using the Schwartz formula for paediatric patients (in mL/min/1.73 m²). Dose is based on CrCL. CrCL should be closely monitored and the dose adjusted according to changing renal function.

^b Ceftaroline is haemodialyzable; thus Zinforo should be administered after haemodialysis on haemodialysis days.

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. No data are available

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).

Severe cutaneous adverse reactions (SCARs), including 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 association with beta-lactam antibiotics (including cephalosporins) treatment

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftaroline fosamil. Ceftaroline should be used with caution in patients with a history of non-severe hypersensitivity reactions to any other beta-lactam antibiotics (e.g. penicillins or carbapenems). If a severe allergic reaction or SCAR occurs during treatment 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 11.2% in the five 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.

Paediatric population

As with adults, the interaction potential is expected to be low in paediatrics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of 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 risk to the newborns/ infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zinforo therapy taking into account the benefit of breast-feeding for the child and 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

Undesirable effects e.g. dizziness may occur and this may have an effect on the ability to drive and use of machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions occurring in $\geq 3\%$ of approximately 3,242 patients treated with Zinforo in clinical studies were diarrhoea, headache, nausea, and pruritus, and were generally mild or moderate in severity. *Clostridium difficile*-associated disease (CDAD) and severe hypersensitivity reactions may also occur.

A greater incidence of rash in Asian patients (see below) and a greater incidence of DAGT seroconversion (see section 4.4) were observed in a study of adult patients with cSSTI conducted with Zinforo 600 mg administered over 120 minutes every 8 hours.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), 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
Infections and infestations			<i>Clostridium difficile</i> colitis (see section 4.4)	

System organ class	Very common	Common	Uncommon	Rare
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)		

System organ class	Very common	Common	Uncommon	Rare
Investigations	Coombs Direct Test Positive (see section 4.4)			

Description of selected adverse reactions

Severe Cutaneous Adverse Reactions

SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis) have been reported with beta-lactam antibiotics, including cephalosporins (see section 4.4).

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 paediatric patients 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 patients 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

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 and penems, ATC code: J01DI02

The active moiety after Zinforo administration is ceftaroline.

Mechanism of action

Ceftaroline is a cephalosporin antibacterial with *in vitro* activity against Gram-positive and -negative bacteria. The bactericidal action of ceftaroline is mediated through binding to essential penicillin-binding proteins (PBPs). Biochemical studies have shown that ceftaroline has high affinity for PBP2a of methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x of penicillin non-susceptible *Streptococcus pneumoniae* (PNSP). 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 (\leq S)	Resistant (R $>$)
<i>Staphylococcus aureus</i>	1 ¹	$>2^2$
<i>Streptococcus pneumoniae</i>	0.25	0.25
<i>Streptococcus</i> Groups A, B, C, G	Note ²	Note ²
<i>Haemophilus influenzae</i>	0.03	0.03
<i>Enterobacteriaceae</i>	0.5	0.5

1. Refers to dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 12 hours using 1-hour infusions (see section 4.2). Note that: There are no clinical trial data regarding the use of ceftaroline to treat CAP due to *S. aureus* with ceftaroline MICs > 1 mg/L

2. Infer susceptibility from susceptibility to benzylpenicillin.

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 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*

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 8 or 12 hours for up to 14 days in healthy adults with CrCL > 50 mL/min.

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 \leq 50 mL/min (see section 4.2).

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

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.

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 test, 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 observed in all groups, including controls, on PND50. The cysts involved a small portion of the kidney and occurred 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

L-Arginine

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

After reconstitution:

The reconstituted vial should be diluted 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 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml glass vial (Type 1) closed with a rubber (bromobutyl) 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.

Zinfofo 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

~~ACS Dobfar S.p.A~~ ~~Facta Farmaceutici S.P.A.~~, Nucleo Industriale S.atto ~~S.niccolo a Tordino~~ 64100 Teramo, Italy

8. MARKETING AUTHORISATION HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzeliya Pituach 46725

9. MARKETING AUTHORISATION NUMBER(S)

150-76-33887

Revised in ~~May~~ July 2020