SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

Zinforo® 600 mg (Powder for concentrate for solution for infusion).

COMPOSITION:

Each vial contains 600 mg ceftaroline fosamil equivalent to 530 mg ceftaroline.

List of excipients: L-arginine.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

Ceftaroline is a cephalosporin with *in vitro* 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 active against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) due to its affinity for the altered PBPs found in these organisms.

Pharmacokinetic/pharmacodynamic relationship:

The percent time above the minimum inhibitory concentration (MIC) of the infecting organism over the dosing interval (% T > MIC) has been shown to best correlate with the antimicrobial activities for ceftaroline.

Mechanisms of resistance:

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

Most isolates of *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas putida*, *Acinetobacter baumannii*, *Acinetobacter* spp, *Stenotrophonomas maltophilia*, *Burkholderia cepacia*, *Bacteroides fragilis* and *Bacteroids thetaiotamicron* are intrinsically resistant to ceftaroline.

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections (see "INDICATIONS").

Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

Pharmacokinetic Properties:

The C_{max} and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50-1 000 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 litres, 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 P450 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 radiolabelled 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 adjustment is required in patients with moderate renal impairment (CrCL) > 30-50 ml/min). 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.

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, 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 33 % increase in $AUC_{0-\infty}$ in the elderly that was mainly attributable to age-related changes in renal function.

Dose adjustment is not required in elderly patients with creatinine clearance (CrCl) above 50 ml/min.

Paediatric patients:

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

INDICATIONS:

ZINFORO is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms.

- **Acute Bacterial Skin and Skin Structure Infections**

ZINFORO is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and - resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumonia and Klebsiella oxytoca.*

- **Community-Acquired Bacterial Pneumonia**

ZINFORO is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteraemia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumonia* and *Escherichia coli.*

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to the cephalosporin class of antibacterials.

Hypersensitivity to any other type of beta-lactam antibacterial agent (e.g. penicillins or carbapenems).

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity reactions:

Serious and fatal hypersensitivity reactions have been reported in patients receiving beta-lactam antibacterials, such as ZINFORO.

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ZINFORO. Before initiating therapy with ZINFORO, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibacterials. If a severe allergic reaction occurs, ZINFORO should be discontinued and appropriate measures taken (see "CONTRAINDICATIONS").

Clostridium difficile-associated diarrhoea:

Antibacterial-associated colitis and pseudomembranous colitis have been reported with 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 ZINFORO. 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:

Convulsions have been reported with ZINFORO.

Clinical study experience with ZINFORO 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 ZINFORO. The incidence of DAGT seroconversion in patients receiving ZINFORO was 10,7 % in the pooled Phase 3 studies. There was no evidence of haemolysis in any patient receiving ZINFORO who developed a positive DAGT.

Patients with renal impairment:

Clinical study experience with ZINFORO in patients with severe renal impairment and ESRD is limited. Therefore, use of ZINFORO is not recommended in these patient populations ("see Pharmacokinetic Properties").

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed.

INTERACTIONS:

No clinical medicine interaction studies have been conducted with ZINFORO.

The interaction potential of ZINFORO on medicines metabolised by P450 enzymes is expected to be low, since ZINFORO is not an inhibitor (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) nor an inducer (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5) of P450 enzymes *in vitro*. ZINFORO is not metabolised by P450 enzymes *in vitro*, so co-administered P450 inducers or inhibitors are unlikely to influence the pharmacokinetics of ZINFORO.

In vitro, ZINFORO is not transported by efflux transporters P-gp (P-glycoprotein) or BCRP (breast cancer resistance protein). ZINFORO does not inhibit P-gp, therefore an interaction with substrates, such as digoxin, is not expected. ZINFORO is a weak inhibitor of BCRP, but the effect is too small to be clinically relevant. *In vitro* studies demonstrated that ZINFORO is not a substrate of, nor did it inhibit the

renal uptake transporters OCT2, OAT1, and OAT3; interactions with medicines that inhibit active renal secretion (e.g. probenecid) or with medicines that are substrates of these transporters would therefore not be expected.

PREGNANCY AND LACTATION:

The safety of ZINFORO in pregnancy and lactation has not been established.

Pregnancy:

No clinical data on pregnancies are available for ZINFORO. ZINFORO should not be used during pregnancy.

Lactation:

It is not known whether ZINFORO is excreted in human milk, but because many beta-lactams are excreted in breast milk, women who are breast-feeding their infants should not be treated with ZINFORO.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dosage of ZINFORO is 600 mg administered every 12 hours by intravenous infusion over 60 minutes in patients ≥ 18 years of age. The duration of treatment should be guided by the type of infection to be treated, its severity, and the patient's clinical response.

Recommended dosage and administration by infections is as follows:

Infection	**Dosage**	**Frequency**	**Infusion time (minutes)**	**Recommended duration of antimicrobial treatment**
Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	600 mg	every 12 hours	60	5-14 days

Community-acquired bacterial pneumonia (CABP)	600 mg	every 12 hours	60	5-7 days

Special populations:

Patients with renal impairment:

The following dose adjustment is recommended in patients with renal impairment (see "WARNINGS AND SPECIAL PRECAUTIONS" and "Pharmacokinetic properties"):

Estimated creatinine clearance (ml/min)	**Recommended dosage regimen**
> 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, including patients undergoing haemodialysis

Patients with hepatic impairment:

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

Elderly patients:

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

Paediatric patients:

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

Instructions for use, handling and disposal:

The powder must be constituted and the resulting concentrate must then be immediately diluted prior to use.

Standard aseptic techniques should be used for solution preparation and administration.

After constitution:

ZINFORO powder for solution for infusion should be constituted with 20 ml of sterile water for injections. The constitution time of the powder should not be more than 120 seconds. The resulting constituted solution must then be immediately diluted prior to use. One ml of the constituted solution contains 30 mg of ceftaroline fosamil. The total time interval between starting constitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

After dilution:

The contents of the vial should be transferred to an infusion bag or bottle for further dilution. The resulting solution should be shaken prior to being transferred to an intravenous bag or bottle.
Compatibility has been demonstrated with 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) or
- lactated Ringer's solution.

ZINFORO must not be mixed with any other medicinal product except those mentioned above.

For storage conditions of the constituted and diluted medicinal product (see "STORAGE INSTRUCTIONS").

Each vial is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE EFFECTS:

Clinical experience:

The 4 clinical trials (2 in ABSSSI and 2 in CABP) included 1305 adult patients treated with ZINFORO (600 mg administered over 60 minutes every 12 hours).

The incidence of treatment emergent adverse events in the pooled ABSSSI and CABP studies was 45,7 %. The most common adverse reactions occurring in ≥ 3 % of patients treated with ZINFORO were diarrhoea, headache, nausea, and pruritus.

The following adverse reactions have been identified during clinical trials with ZINFORO. Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are derived from the adverse events observed in the pooled and CAP studies and are defined according to the following conventions:
Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000).

Frequency of adverse reactions in clinical trials:

Frequency	System organ class	Event
Very common (≥ 10 %)	Investigations	Coombs Direct Test Positive (see "WARNINGS AND SPECIAL PRECAUTIONS")
Common (≥ 1 % and < 10 %)	Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain

	Nervous system disorders	Headache, dizziness
	Skin and subcutaneous tissue disorders	Rash, pruritus
	Hepatobiliary disorders	Increased transaminases
	Vascular disorders	Phlebitis
	General disorders and administration site conditions	Pyrexia
Uncommon (≥ 0,1 % and < 1 %)	Blood and lymphatic system disorders	Anaemia, thrombocytopenia
	Immune system disorders	Hypersensitivity/anaphylaxis (See "CONTRAINDICATIONS" and WARNINGS AND SPECIAL PRECAUTIONS")
	Skin and subcutaneous tissue disorders	Urticaria
	Infections and infestation	*Clostridium difficile* colitis (see "WARNINGS AND SPECIAL PRECAUTIONS")
	Investigations	Prothrombin time prolonged, international normalized ratio increased
	Renal and urinary disorders	Blood creatinine increased
	General disorders and administration site conditions	Infusion site reactions (erythema, phlebitis, pain)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosing can occur particularly in patients with moderate to severe renal impairment.

Treatment should be symptomatic and supportive.

ZINFORO can be partially removed by haemodialysis.

IDENTIFICATION:

A pale yellowish-white to light yellow powder, sterile and pyrogen free.

PRESENTATION:

Powder in a glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap. Supplied in packs of 10 vials.

STORAGE INSTRUCTIONS: Store at or below 25 °C.

ZINFORO solution for infusion can be administered in a 50 ml, 100 ml or 250 ml intravenous bag or bottle.

Once the intravenous solution is prepared in the intravenous bag or bottle it should be administered within 6 hours of preparation.

Chemical and physical in-use stability has been demonstrated for 6 hours at 25 ºC and 24 hours at 2 to 8 ºC. From a microbiological point of view, the 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 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

REGISTRATION NUMBER:

46/20.1.1/0628

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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