SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZAVICEFTA® 2 g/0,5 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0,5 g avibactam.

After reconstitution, 1 mL of solution contains 167,3 mg of ceftazidime and 41,8 mg of avibactam (see section 6.6).

Sugar free.

Excipients with known effect

Each vial contains 6,44 mmol (approximately 146 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A white to pale yellow sterile powder.

The reconstituted solution is a clear and colourless to yellow solution free from visible particulate matter.

ZAVICEFTA is sterile, pyrogen-free and free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZAVICEFTA is indicated in adults and paediatric patients 3 months of age and older for the treatment of infections caused by designated susceptible Gram-negative microorganisms (see section 4.4 and section 5.1).

ZAVICEFTA should be reserved for the treatment of Gram-negative infections in adults and paediatric patients 3 months of age and older, caused by Gram-negative sensitive bacteria where other antimicrobials approved for similar infections and to which a causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or were not tolerated.

- Complicated intra-abdominal infections (cIAI), used in combination with metronidazole. (*Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Pseudomonas aeruginosa*).
- Complicated urinary tract infections (cUTI), including pyelonephritis. (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Pseudomonas aeruginosa*).
- Hospital-acquired bacterial pneumonia (HABP). (*Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Serratia marcescens, Pseudomonas aeruginosa*).
- Ventilator associated bacterial pneumonia (VABP). (*Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Serratia marcescens, Pseudomonas aeruginosa*).

Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

4.2 Posology and method of administration

Posology

Adults

The recommended dosage of ZAVICEFTA is 1 vial where each vial contains 2 g ceftazidime and 0,5 g avibactam administered by intravenous (IV) infusion in a volume of 100 mL at a constant rate over 120 minutes in patients aged 18 years or older. Treatment is repeated every 8 hours. For adults with renal impairment where CrCl ≤ 50 mL/min, see dosing recommendations in Table 2.

Dosage in adults with creatinine clearance (CrCL) > 50 mL/min

Table 1 shows the recommended intravenous dose for adults with estimated creatinine clearance (CrCL) > 50 mL/min (see sections 4.4 and 5.1).

Table 1: Recommended dose for adults with estimated CrCL > 50 mL/min[1]

Type of infection	**Dose of ceftazidime/ avibactam**	**Frequency**	**Infusion time**	**Duration of treatment**
cIAI[2,3]	2 g/0,5 g	Every 8 hours	2 hours	5 - 14 days
cUTI, including pyelonephritis[3]	2 g/0,5 g	Every 8 hours	2 hours	5 - 10 days[4]
HAP/VAP[3]	2 g/0,5 g	Every 8 hours	2 hours	7 - 14 days
Bacteraemia associated with, or suspected to be associated with any of the above infections	2 g/0,5 g	Every 8 hours	2 hours	Duration of treatment should be in accordance with the site of infection.

[1] CrCL estimated using the Cockcroft-Gault formula.

[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[3] To be used in combination with an antibacterial medicine active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

[4] The total duration shown may include intravenous ZAVICEFTA followed by appropriate oral therapy. The time to switch from intravenous ZAVICEFTA to oral treatment with another antibiotic depends on the clinical situation but is normally after about 5 days (the minimum duration of treatment with ZAVICEFTA in clinical trials was 5 days).

For complicated urinary tract infection (cUTI) including pyelonephritis, the total duration of treatment could be increased to 14 days for patients with bacteraemia.

The duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Special populations

Elderly patients

No dosage adjustment is considered necessary in elderly patients (≥ 65 years). The dose regimen should be adjusted if renal impairment is present (see section 5.2).

Adults with renal impairment

The following dose adjustment is recommended in patients with renal impairment (see sections 4.4 and 5.2).

Dose adjustments for ZAVICEFTA for patients with an estimated creatinine clearance (CrCl) ≤ 50 mL/min are outlined in Table 2 below. The only information on dosing of ZAVICEFTA for patients requiring dialysis is in the setting of intermittent haemodialysis. For other types of dialysis, it is suggested that the dose/frequency of ZAVICEFTA should follow local label/local guidelines for dosing of ceftazidime. For example, for a dose of 500 mg ceftazidime the dose of ZAVICEFTA would be 500 mg ceftazidime/125 mg avibactam.

Table 2: Recommended dose for adults with estimated CrCL[1] ≤ 50 mL/min

Age Group	Estimated CrCL (mL/min)	Dose of ceftazidime/ avibactam[2,4]	Fre-quency	Infusion time
Adults	31 - 50	1 g/0,25 g	Every 8 hours	2 hours
	16 - 30	0,75 g/0,1875 g	Every 12 hours	
	6 - 15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1] CrCL estimated using the Cockcroft-Gault formula.

[2] Dose recommendations are based on pharmacokinetic modelling (see section 5.2).

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). Dosing of ZAVICEFTA on haemodialysis days should occur after completion of haemodialysis.

[4] ZAVICEFTA is a combination medicine in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).

Haemodialysis

Both ceftazidime and avibactam are haemodialysable; thus, ZAVICEFTA should be administered after haemodialysis on haemodialysis day.

Haemofiltration

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing continuous veno-venous haemofiltration.

Peritoneal dialysis

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing peritoneal dialysis.

Patients with hepatic impairment

No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2). Close clinical monitoring for safety and efficacy is advised.

Paediatric patients

The safety and efficacy of ZAVICEFTA in paediatric patients < 3 months old have not been established. No data are available.

Dosage in paediatric patients with creatinine clearance (CrCL) > 50 mL/min/1,73 m^2

Table 3 shows the recommended intravenous doses for paediatric patients with estimated creatinine clearance (CrCL) > 50 mL/min/1,73 m^2 (see sections 4.4 and 5.1).

Table 3: Recommended dose for paediatric patients with estimated CrCL[1] > 50 mL/min/1,73 m^2

Type of infection	**Age group**	**Dose of ceftazidime/ avibactam[6]**	**Fre-quency**	**Infu-sion time**	**Duration of treatment**
cIAI[2,3] OR cUTI including pyelonephritis[3] OR	6 months to < 18 years	50 mg/kg/12,5 mg/kg to a maximum of 2 g/0,5 g	Every 8 hours	2 hours	cIAI: 5 – 14 days cUTI[4]: 5 – 14 days HAP/VAP: 7 – 14 days
HAP/VAP[3]	3 months to < 6 months[5]	40 mg/kg/10 mg/kg	Every 8 hours	2 hours	

[1] CrCL estimated using the Schwartz bedside formula.

[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[3] To be used in combination with an antibacterial medicine active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

[4] The total treatment duration shown may include intravenous ZAVICEFTA followed by appropriate oral therapy.

[5] There is limited experience with the use of ZAVICEFTA in paediatric patients 3 months to < 6 months (see section 5.2).

[6] ZAVICEFTA is a combination medicine in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).

Table 4 and Table 5 show the recommended dose adjustments for paediatric patients with estimated CrCL ≤ 50 mL/min/1,73 m^2 according to different age groups (see sections 4.4 and 5.2).

Dosage in paediatric patients ≥ 2 years of age with CrCL ≤ 50 mL/min/1,73 m²

Table 4: Recommended dose for paediatric patients with estimated CrCL[1] ≤ 50 mL/min/1,73 m²

Age Group	Estimated CrCL (mL/min/1,73 m²)	Dose of ceftazidime/ avibactam[2,4]	Frequency	Infusion time
Paediatric patients 2 of age to < 18 years	31 - 50	25 mg/kg/6,25 mg/kg to a maximum of 1 g/0,25 g	Every 8 hours	2 hours
	16 - 30	18,75 mg/kg/4,7 mg/kg to a maximum of 0,75 g/0,1875 g	Every 12 hours	
	6 - 15		Every 24 hours	
	End Stage Renal Disease including on haemodialysis[3]		Every 48 hours	

[1] CrCL estimated using the Schwartz bedside formula.

[2] Dose recommendations are based on pharmacokinetic modelling (see section 5.2).

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). Dosing of ZAVICEFTA on haemodialysis days should occur after completion of haemodialysis.

[4] ZAVICEFTA is a combination medicine in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).

Dosage in paediatric patients < 2 years of age with CrCl ≤ 50 mL/min/1,73 m²

Table 5: Recommended dose for paediatric patients with estimated CrCL[1] ≤ 50 mL/min/1,73 m²

Age Group	**Estimated CrCL (mL/min/ 1,73 m^2)**	**Dose of ceftazidime/avibactam[2,3]**	**Frequency**	**Infusion time**
3 to < 6 months	31 - 50	20 mg/kg/5 mg/kg	Every 8 hours	2 hours
6 months to < 2 years		25 mg/kg/6,25 mg/kg	Every 8 hours	
3 to < 6 months	16 - 30	15 mg/kg/3,75 mg/kg	Every 12 hours	
6 months to < 2 years		18,75 mg/kg/4,7 mg/kg	Every 12 hours	

[1] Calculated using the Schwartz bedside formula.

[2] Dose recommendations are based on pharmacokinetic modelling (see section 5.2).

[3] ZAVICEFTA is a combination medicine in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).

There is insufficient information to recommend a dosage regimen for paediatric patients < 2 years of age that have a CrCL < 16 mL/min/1,73 m^2.

Method of administration

For intravenous use.

ZAVICEFTA is administered by intravenous infusion over 120 minutes in an appropriate infusion volume of 100 mL.

For instructions on reconstitution and dilution before administration of ZAVICEFTA, see section 6.6.

4.3 Contraindications

- Hypersensitivity to ceftazidime, avibactam or to any of the excipients contained in ZAVICEFTA (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 β-lactam antibacterial medicine (e.g. penicillins, monobactams or carbapenems).

4.4 Special warnings and precautions for use

Antibiotic stewardship

Prescribers should adhere to the principles of antimicrobial stewardship.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZAVICEFTA, ZAVICEFTA should be used to treat only indicated infections that are proven or strongly suspected to be caused by susceptible bacteria. It is recommended that ZAVICEFTA be used only after consultation with a medical practitioner with appropriate experience in the management of infectious diseases.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported (see sections 4.3 and 4.8). In severe hypersensitivity reactions, treatment with ZAVICEFTA must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam medicine. Caution should be used if ZAVICEFTA is given to patients with a history of non-severe hypersensitivity to other β-lactam medicines.

Clostridium difficile-associated diarrhoea

Antibacterial medicine-associated colitis and pseudo-membranous colitis have been reported with ZAVICEFTA 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 ZAVICEFTA (see section 4.8). Discontinuation of therapy with ZAVICEFTA and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Patients with renal impairment

Ceftazidime and avibactam are eliminated via the kidneys; therefore, the dose of ZAVICEFTA should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have been reported with ceftazidime when the dose has not been reduced in patients with renal impairment (see section 4.2).

In patients with impaired renal function, regular monitoring of estimated creatinine clearance is advised as in some patients, especially early in the course of their infection, the creatinine clearance estimated from serum creatinine can change quickly.

Nephrotoxicity

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.

Non-susceptible organisms

Prolonged use of ZAVICEFTA may result in the overgrowth of non-susceptible organisms (e.g. enterococci, fungi), which may require interruption of treatment or other appropriate measures.

Non-medicine interference

Ceftazidime does not interfere with enzyme-based tests for glycosuria, but slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia

ZAVICEFTA use may cause development of a positive direct antiglobulin test (DAGT, or Coombs test), which may interfere with the cross-matching of blood and/or may cause medicine induced immune haemolytic anaemia. While DAGT seroconversion in patients receiving ZAVICEFTA was frequent in clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment (see section 4.8). However, the possibility that haemolytic anaemia could occur in association with ZAVICEFTA treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with ZAVICEFTA should be investigated for this possibility.

Controlled sodium diet

For patients who are on a controlled sodium diet, the following important information about the ingredients of ceftazidime and avibactam should be considered:

- 2 g powder for solution for infusion - ceftazidime 2 g contains 4,52 mmol of sodium per vial; and
- 500 mg powder for solution for infusion - avibactam 500 mg contains 1,92 mmol of sodium per vial.

ZAVICEFTA contains approximately 146 mg sodium per vial, equivalent to 7,3 % of the WHO recommended maximum daily intake (RDI) of 2 g sodium for an adult.

The maximum daily dose of this medicine is equivalent to 22 % of the WHO recommended maximum daily intake for sodium. ZAVICEFTA is considered high in sodium. This should be considered when administering ZAVICEFTA to patients who are on a controlled sodium diet.

ZAVICEFTA may be diluted with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Paediatric population

There is a potential risk of overdosing, particularly for paediatric patients from 3 of age to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose (see sections 4.9 and 6.6).

4.5 Interaction with other medicines and other forms of interaction

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function (see section 4.4).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ZAVICEFTA with chloramphenicol is proposed, the possibility of antagonism should be considered.

Avibactam showed no significant inhibition of cytochrome P450 enzymes. Avibactam and ceftazidime showed no *in vitro* cytochrome P450 induction in the clinically relevant exposure range. Avibactam and ceftazidime do not inhibit the major renal or hepatic transporters in the clinically relevant exposure range, therefore the drug-drug interaction potential via these mechanisms is considered low.

In vitro, avibactam is a substrate of OAT1 (organic anion transporter) and OAT3 transporters which might contribute to the active uptake from the blood compartment and, thereby its excretion. Probenecid (a potent OAT inhibitor) inhibits this uptake by 56 % to 70 % *in vitro* and, therefore, has the potential to alter the elimination of avibactam when co-dosed. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-dosing of avibactam with probenecid is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been established. Following administration of avibactam throughout pregnancy and lactation in the rat at maternal exposures greater than or equal to approximately 1,5 times human therapeutic exposures, there were minor changes in the morphology of the kidney and ureters in the rat pups.

ZAVICEFTA should not be used during pregnancy unless clearly necessary.

Breastfeeding

Ceftazidime is excreted in human milk. Avibactam is excreted in rodent milk; it is unknown whether avibactam is excreted in human milk. Women receiving ZAVICEFTA should not breastfeed their infants.

Fertility

The effects of ZAVICEFTA on fertility in humans have not been studied. Animal studies with ceftazidime or avibactam do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In seven phase 2 and phase 3 clinical trials, 2 024 adult patients were treated with ZAVICEFTA. The most common adverse reactions occurring in ≥ 5 % of patients treated with ZAVICEFTA were a positive direct antiglobulin test (DAGT), nausea, and diarrhoea. These were usually mild or moderate in intensity. No clinically significant differences were observed in the safety profile across indications.

Tabulated list of adverse reactions
The following adverse reactions have been reported with ceftazidime alone and/or identified during all Phase 2 and Phase 3 clinical trials with ZAVICEFTA (n=2 024). Adverse reactions are classified according to frequency and system organ class. Frequency categories are derived from adverse reactions and/or potentially clinically significant laboratory abnormalities, and are defined according to the following conventions:

Very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1 000 and <1/100); rare (≥ 1/10 000 and < 1/1 000); very rare (< 1/10 000); unknown (cannot be estimated from the available data).

If an event was not seen in the overall Phase 2 and Phase 3 pool but was a known adverse reaction for ceftazidime alone, the frequency category for ceftazidime alone was used (including the category unknown).

Table 6: Frequency of adverse reactions by system organ class

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Candidiasis (including vulvovaginal candidiasis and oral candidiasis)
	Uncommon	*Clostridium difficile* colitis, pseudomembranous colitis
Blood and lymphatic system disorders	Very common	Positive direct antiglobulin test (DAGT) (see section 4.4)
	Common	Eosinophilia, thrombocytosis, thrombocytopenia
	Uncommon	Neutropenia, leukopenia, lymphocytosis
	Unknown	Agranulocytosis, haemolytic anaemia
Immune system disorders	Unknown	Anaphylactic reaction
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Paraesthesia
Gastrointestinal disorders	Common	Diarrhoea, abdominal pain, nausea, vomiting
	Uncommon	Dysgeusia
Hepatobiliary disorders	Common	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased Gamma-glutamyltransferase, increased blood lactate dehydrogenase
	Unknown	Jaundice
Skin and subcutaneous tissue disorders	Common	Maculopapular rash, urticaria, pruritus
	Unknown	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema,

		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders	Uncommon	Increased blood creatinine, increased blood urea, acute kidney injury
	Very rare	Tubulointerstitial nephritis
General disorders and administration site conditions	Common	Infusion site thrombosis, infusion site phlebitis, pyrexia

Paediatric population

The safety assessment in paediatric patients is based on the safety data from two trials in which 61 patients (from 3 to less than 18 years of age) with cIAI and 67 patients with cUTI (from 3 months to less than 18 years of age) received ZAVICEFTA. Overall, the safety profile in these 128 paediatric patients was similar to that observed in the adult population with cIAI and cUTI.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosing with ZAVICEFTA can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

Symptomatic and supportive treatment for overdose should follow local standard medical practice. Both ceftazidime and avibactam can be partially removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ceftazidime, combinations, ATC code: J01DD52

Mechanism of action

Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following attachment to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. This broad spectrum cephalosporin is active against many Gram-negative and Gram-positive bacterial pathogens *in vitro*.

Avibactam is a non β-lactam, β-lactamase inhibitor that acts by forming a covalent adduct with the enzyme that is stable to hydrolysis. It inhibits both Ambler class A and class C β-lactamases, including extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and AmpC enzymes. Avibactam also inhibits the class D carbapenemase OXA-48, which does not significantly hydrolyse ceftazidime. Avibactam has no clinically relevant *in vitro* antibacterial activity. Avibactam did not induce transcription of bla_{AmpC} in *Enterobacter cloacae*, *Citrobacter freundii* or *Pseudomonas aeruginosa in vitro* at concentrations used to treat patients.

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.

The susceptibility to ceftazidime-avibactam 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.

Pharmacokinetic/pharmacodynamic relationship

The antimicrobial activity of ceftazidime-avibactam against specific pathogens has been shown to best correlate with the percent time of free medicine concentration above the ceftazidime-avibactam minimum inhibitory concentration (MIC) over

the dose interval (% *f*T > MIC of ceftazidime-avibactam) for ceftazidime, and the percent time of the free medicine concentration above a threshold concentration over the dose interval (% *f*T > C_T) for avibactam.

Mechanism of resistance

Ceftazidime-avibactam is not active against metallo-β-lactamase-producing bacteria. Bacterial resistance mechanisms that could potentially affect ceftazidime-avibactam include mutant or acquired PBPs, decreased outer membrane permeability to either compound, active efflux of either compound, mutated or acquired β-lactamase enzymes insensitive to avibactam and able to hydrolyse ceftazidime.

Cross-resistance

There is cross-resistance with β-lactam antibacterial medicines, including carbapenems, when the mechanism is production of metallo-β-lactamases, such as VIM-2.

Interaction with other antimicrobial medicines

In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonise or be antagonised by other antibiotics of various classes (e.g. metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin, tigecycline).

Paediatric population

Ceftazidime-avibactam has been evaluated in paediatric patients 3 months of age to < 18 years in two Phase 2 single-blind, randomised, comparative clinical studies, one in patients with cIAI and one in patients with cUTI. The primary objective in each study was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of pharmacokinetics and efficacy; efficacy was a descriptive endpoint in both studies. Clinical cure rate at TOC (ITT) was 91,8 % (56/61) for ceftazidime-avibactam compared to 95,5 % (21/22) for the comparator in paediatric patients with cIAI. Microbiological eradication rate at TOC (micro-ITT) was 79,6 % (43/54) for ceftazidime-avibactam compared to 60,9 % (14/23) for the comparator in paediatric patients with cUTI.

5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is low, approximately 10 % and 8 %, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were comparable, about 22 L and 18 L respectively in healthy adults following multiple doses of 2 000 mg/500 mg ceftazidime-avibactam infused over 2 hours every 8 hours. Pharmacokinetic parameters of ceftazidime and avibactam following single and multiple dose administration of ZAVICEFTA were similar to those determined when ceftazidime or avibactam were administered alone. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30 % that of plasma, and a similar concentration time profile between ELF and plasma.

Ceftazidime and avibactam plasma exposure were comparable across patients with different indications, complicated intra-abdominal infections (cIAI complicated urinary tract infections (cUTI) including pyelonephritis, hospital-acquired bacterial pneumonia (HABP) and ventilator associated bacterial pneumonia (VABP).

Penetration of ceftazidime into the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the cerebrospinal fluid (CSF) in the absence of inflammation. However, concentrations of 4 to 20 mg/L or more are achieved in the CSF when the meninges are inflamed. Avibactam penetration of the blood brain barrier has not been studied clinically; however, in rabbits with inflamed meninges, CSF exposures of ceftazidime and avibactam were 43 % and 38 % of plasma area under the curve (AUC), respectively. For ceftazidime, concentrations in excess of the MIC of ceftazidime-avibactam for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily and is excreted in the breast milk. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free medicine concentrations in plasma.

Biotransformation

Ceftazidime is not metabolised. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes). Unchanged avibactam was the major medicine-related component in human plasma and urine following dosing with [^{14}C]-avibactam.

Elimination

The terminal half-life (t½) of both ceftazidime and avibactam is about 2 hours after IV administration. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 - 90 % of the dose is recovered in the urine within 24 hours. Avibactam is excreted unchanged into the urine with a renal clearance of approximately 158 mL/min, suggesting active tubular secretion in addition to glomerular filtration; approximately 97 % of the dose is recovered in the urine, 95 % within 12 hours. Less than 1 % of ceftazidime is excreted via the bile and less than 0,25 % of avibactam is excreted into faeces.

Linearity/non-linearity

The pharmacokinetics of both ceftazidime and avibactam are approximately linear across the dose range studied (50 mg to 2 000 mg) for a single IV administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple IV infusions of 2 000 mg/500 mg of ceftazidime-avibactam administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Special populations

Patients with renal impairment

Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment, and end stage renal disease including patients undergoing haemodialysis (Table 7); the dose should be reduced in patients with creatinine clearance (CrCl) ≤ 50 mL/min (see section 4.2).

Table 7. Ceftazidime and avibactam PK parameters (geometric mean) in individuals with varying degrees of renal function

		Renal function			
	PK para-meter	**Mild impairment (CrCl 50 - 79 mL/min)**	**Moderate impairment (CrCl 30 - 49 mL/min)**	**Severe impairment (CrCl < 30 - 6 mL/min)**	**ESRD (CrCl < 6 mL/min) Off dialysis**
Ceftazidime	t½ (h)	2,49	3,74	7,41	24,6
	CL (L/h)	3,24	3,14	1,52	0,45
Avibactam	t½ (h)	4,00	5,23	7,66	22,82
	CL (L/h)	5,70	3,90	2,12	0,77
CL - Total body clearance of medicine from plasma; CrCl - Creatinine clearance; ESRD - End stage renal disease; PK - Pharmacokinetic; t½ -Terminal elimination half-life.					

Patients with hepatic impairment

Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g IV every 8 hours for 5 days, provided renal function was not impaired. The pharmacokinetics of ceftazidime in patients with severe hepatic impairment has not been established. The pharmacokinetics of avibactam in patients with any degree of hepatic impairment has not been studied.

As ceftazidime and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either medicine is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ceftazidime-avibactam is recommended for patients with hepatic impairment (see section 4.2).

Elderly patients

The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3,5 to 4 hours following single or 7 days repeated every 12 hours dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Following single dose IV administration of 500 mg avibactam as a 30-minute IV infusion, the elderly had a slower terminal half-life of avibactam, which may be attributed to age related decrease in renal clearance. Dosage adjustment for ceftazidime-avibactam is not required in elderly individuals (≥ 65 years of age) with CrCl > 50 mL/min.

Paediatric patients

The pharmacokinetics of ceftazidime and avibactam were evaluated in paediatric patients from 3 months to < 18 years of age with suspected or confirmed infections following a single dose of ceftazidime 50 mg/kg and avibactam 12,5 mg/kg for patients weighing < 40 kg or ceftazidime-avibactam 2 g/0,5 g (ceftazidime 2 grams and avibactam 0,5 grams) for patients weighing ≥ 40 kg. Plasma concentrations of ceftazidime and avibactam were similar across all four age cohorts in the study (3 months to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Ceftazidime and avibactam AUC_{0-t} and C_{max} values in the two older cohorts (paediatric patients from 6 to < 18 years), which had more extensive pharmacokinetic sampling, were similar to those observed in healthy adult individuals with normal renal function that received ceftazidime-avibactam 2 g/0,5 g. Data from this study and the two Phase 2 paediatric studies in patients with cIAI and cUTI were pooled with PK data from adults (Phase 1 to Phase 3) to update the population PK model, which was used to conduct simulations to assess PK/PD target attainment. Results from these simulations demonstrated that the recommended dose regimens for paediatric patients with cIAI, cUTI and HAP/VAP, including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adults at the approved ceftazidime-avibactam dose of 2 g/0,5 g administered over 2 hours, every 8 hours.

There is limited experience with the use of ceftazidime plus avibactam in the paediatric groups of 3 months to < 6 months of age. The recommended dosing regimens are based on simulations conducted using the final population PK models. Simulations demonstrated that the recommended dose regimens result in comparable exposures to other age groups with

PK/PD target attainment > 90 %. Based on data from the completed paediatric clinical trials, at the recommended dose regimens, there was no evidence of over or under exposure in the individuals 3 months to < 6 months of age.

In addition, there is very limited data in paediatric patients 3 months to < 2 years of age with impaired renal function (CrCL ≤ 50 mL/min/1,73 m^2), with no data in severe renal impairment from the completed paediatric clinical trials. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous)

6.2 Incompatibilities

ZAVICEFTA must not be mixed with other medicines or solutions except those mentioned in section 6.6.

6.3 Shelf life

Dry powder

3 years.

After reconstitution

The reconstituted vial should be used immediately.

After dilution

Infusion bags

Once the intravenous solution is prepared with diluents listed above, it should be administered within 12 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 the diluted medicine must be stored at room temperature and used within 12 hours.

From a microbiological point of view, ZAVICEFTA 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 - 8 ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Infusion syringes

The chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 6 hours at no more than 25 °C.

From a microbiological point of view, the medicine should be used immediately unless reconstitution and dilution have 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 and must not exceed 6 hours at no more than 25 °C.

6.4 Special precautions for storage

Store at or below 30 °C.

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

For storage conditions of the reconstituted and diluted medicine, see section 6.3.

6.5 Nature and contents of container

20 mL clear glass vial (Type 1) closed with a grey rubber (bromobutyl) stopper and aluminium flip-off overseal cap. The flip-off cap is light blue in colour.

ZAVICEFTA is supplied in packs of 10 vials. Vials are packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

The powder must be reconstituted with sterile 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.

ZAVICEFTA is a combination medicine; each vial contains 2 g of ceftazidime and 0,5 g of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only.

Standard aseptic techniques should be used for solution preparation and administration. Doses may be prepared in an appropriately sized infusion bag or infusion syringe.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

Each vial is for single use only.

The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

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

Instructions for preparing adult and paediatric doses in infusion bag or in infusion syringe:

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 8 - 40 mg/mL of ceftazidime. All calculations should be completed prior to initiating these steps. For paediatric patients aged 3 to 12 months, detailed steps to prepare a 20 mg/mL concentration (sufficient for most scenarios) are also provided.

1. Prepare the reconstituted solution (167,3 mg/mL of ceftazidime):
    a. Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injection.
    b. Withdraw the needle and shake the vial until the content dissolves to give a clear solution.
    c. Do not insert a gas relief needle until the medicine has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure. Note: To preserve medicine sterility, it is important that the gas relief needle is not inserted through the vial closure before the medicine is dissolved.

2. Prepare the final solution for infusion (final concentration must be 8 - 40 mg/mL of ceftazidime):
    a. Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution to an infusion bag. An infusion bag may contain any of the following: 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 100 mL infusion bag can be used to prepare the infusion, based on the patient's volume requirements.

b. Infusion syringe: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0,9 %) solution for injection or dextrose 50 mg/mL
(5 %) solution for injection) to an infusion syringe.

Table 8: Preparation of ZAVICEFTA for adult and paediatric doses in infusion bag or in infusion syringe.

ZAVICEFTA Dose (ceftazidime)[1]	**Volume to withdraw from reconstituted vial**	**Final volume after dilution in infusion bag[2]**	**Final volume in infusion syringe**
2 g	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1g	6 mL	25 mL to 125 mL	25 mL to 50 mL
0,75 g	4,5 mL	19 mL to 93 mL	19 mL to 50 mL
All other doses	Volume (mL) calculated based on dose required: Dose (mg ceftazidime) ÷ 167,3 mg/mL ceftazidime	Volume (mL) will vary based on infusion bag size availability and preferred final concentration (must be 8 - 40 mg/mL of ceftazidime)	Volume (mL) will vary based on infusion syringe size availability and preferred final concentration (must be 8 - 40 mg/mL of ceftazidime)

[1] Based on ceftazidime component only.

[2] Dilute to final ceftazidime concentration of 8 mg/mL for in-use stability up to 12 hours at 2 - 8°C, followed by up to 4 hours at not more than 25°C (i.e. dilute 2 g dose of ceftazidime in 250 mL, 1 g dose of ceftazidime in 125 mL, 0.75 g dose of

ceftazidime in 93 mL, etc.). All other ceftazidime concentrations (> 8 mg/mL to 40 mg/mL) have in-use stability up to 4 hours at not more than 25°C.

A dose of 1 000 mg/250 mg or 750 mg/187,5 mg is achieved with 6,0 mL or 4,5 mL aliquots, respectively.

Preparation of ZAVICEFTA for use in paediatric patients aged 3 to 12 months of age in infusion syringe:

NOTE: The following procedure describes the steps to prepare an infusion solution with a final concentration of 20 mg/mL of ceftazidime (sufficient for most scenarios). Alternative concentrations may be prepared,but must have a final concentration range of 8 - 40 mg/mL of ceftazidime.

1. Prepare the reconstituted solution (167,3 mg/mL of ceftazidime):

    a) Insert the syringe needle through the vial closure and inject 10 mL of sterile water for injections.

    b) Withdraw the needle and shake the vial to give a clear solution.

    c) Insert a gas relief needle through the vial closure after the product has dissolved to relieve the internal pressure (this is important to preserve product sterility).

2. Prepare the final solution for infusion to a final concentration of 20 mg/mL of ceftazidime:

    a) Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution combined with a sufficient volume of diluent (sodium chloride 9 mg/mL (0,9 %) solution for injection or dextrose 50 mg/mL (5 %) solution for injection) to an infusion syringe.

    b) Refer to Table 9, 10, or 11 below to confirm the calculations. Values shown are approximate as it may be necessary to round to the nearest graduation mark of an appropriately sized syringe. Note that the tables are NOT inclusive of all possible calculated doses but may be utilized to estimate the approximate volume to verify the calculation.

Table 9: Preparation of ZAVICEFTA (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with creatinine clearance (CrCL) > 50 mL/min/1,73 m^2

Age and ZAVICEFTA Dose (mg/kg)[1]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be withdrawn from vial (mL)	Volume of diluent to add for mixing (mL)
6 months to 12 months 50 mg/kg of ceftazidime	5	250	1,5	11
	6	300	1,8	13
	7	350	2,1	15
	8	400	2,4	18
	9	450	2,7	20
	10	500	3	22
	11	550	3,3	24
	12	600	3,6	27
3 months to < 6 months 40 mg/kg of ceftazidime	4	160	1	7,4
	5	200	1,2	8,8
	6	240	1,4	10
	7	280	1,7	13
	8	320	1,9	14
	9	360	2,2	16
	10	400	2,4	18

[1] Based on ceftazidime component only.

Table 10: Preparation of ZAVICEFTA (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with CrCL 31 to 50 mL/min/1,73 m²

Age and ZAVICEFTA Dose (mg/kg)[1]	Weight (kg)	Dose (mg ceftazidime)	Volume of reconstituted solution to be	Volume of diluent to add for

			withdrawn from vial (mL)	**mixing (mL)**
6 months to 12 months 25 mg/kg of ceftazidime	5	125	0,75	5,5
	6	150	0,9	6,6
	7	175	1	7,4
	8	200	1,2	8,8
	9	225	1,3	9,6
	10	250	1,5	11
	11	275	1,6	12
	12	300	1,8	13
3 months to < 6 months 20 mg/kg of ceftazidime	4	80	0,48	3,5
	5	100	0,6	4,4
	6	120	0,72	5,3
	7	140	0,84	6,2
	8	160	1	7,4
	9	180	1,1	8,1
	10	200	1,2	8,8

[1] Based on ceftazidime component only.

Table 11: Preparation of ZAVICEFTA (final concentration of 20 mg/mL of ceftazidime) in paediatric patients 3 to 12 months of age with CrCL 16 to 30 mL/min/1,73 m²

Age and ZAVICEFTA Dose (mg/kg) [1]	**Weight (kg)**	**Dose (mg ceftazidime)**	**Volume of reconstituted solution to be withdrawn from vial (mL)**	**Volume of diluent to add for mixing (mL)**
6 months to 12 months **18,75 mg/kg of ceftazidime**	5	93,75	0,56	4,1
	6	112,5	0,67	4,9
	7	131,25	0,78	5,7
	8	150	0,9	6,6
	9	168,75	1	7,4
	10	187,5	1,1	8,1
	11	206,25	1,2	8,8
	12	225	1,3	9,6
3 months to < 6 months **15 mg/kg of ceftazidime**	4	60	0,36	2,7
	5	75	0,45	3,3
	6	90	0,54	4
	7	105	0,63	4,6
	8	120	0,72	5,3
	9	135	0,81	6
	10	150	0,9	6,6

[1] Based on ceftazidime component only.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Manufacturer: GlaxoSmithKline Manufacturing S.p.A., Verona, Italy