▼ This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ZAVICEFTA®2000/500 (ceftazidime/avibactam)

1. NAME OF MEDICINE

Ceftazidime (as pentahydrate)/avibactam (as sodium).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime (as pentahydrate) equivalent to 2000 mg ceftazidime and avibactam (as sodium) equivalent to 500 mg avibactam).

After reconstitution, 1 mL of solution contains 167.3 mg of ceftazidime (CAZ) and 41.8 mg of avibactam (AVI).

Ceftazidime (as pentahydrate) is a white to almost white crystalline powder. It is soluble in acid, alkali and dimethyl sulphoxide and slightly soluble in water, methanol and dimethylformamide.

Avibactam (as sodium) is a crystalline powder. It is freely soluble in water, relatively soluble in methanol and insoluble in ethanol.

Excipients with known effect

Each vial contains 6.44 mmol of sodium (approximately 148 mg).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for Injection.

Zavicefta is white to light yellow powder.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zavicefta is indicated for the treatment of the following infections in adults (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties):

- Complicated intra-abdominal infection (cIAI), in combination with metronidazole.
- Complicated urinary tract infection (cUTI), including pyelonephritis.
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Zavicefta should be used in combination with an antibacterial agent(s) active against Gram-positive and/or anaerobic pathogens when these are known or suspected to be contributing to the infectious process.

4.2 Dose and method of administration

Dosage

The recommended dosage is 1 vial where each vial contains 2000 mg ceftazidime and 500 mg avibactam. Treatment is repeated every 8 hours. For patients with renal impairment, see dosage adjustments, renal impairment later in this section.

Table 1: Summary of treatment duration by indication or condition

Type of infection	Frequency	Infusion time	Duration of treatment
Complicated IAI[1, 2]	Every 8 hours	2 hours	5-14 days
Complicated UTI, including pyelonephritis[2]	Every 8 hours	2 hours	5-10 days[3]
Hospital-acquired pneumonia, including VAP[2]	Every 8 hours	2 hours	7-14 days

[1] Used in combination with metronidazole in cIAI clinical trials.

[2] To be used in combination with antibacterial agent(s) active against Gram-positive and/or anaerobic pathogens when these are known or suspected to be contributing to the infectious process.

[3] The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy.

For 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.

Dosage adjustments

Renal impairment

No dosage adjustment is required in patients with mild renal impairment (estimated creatinine clearance (CrCL) ³ 51 £ 80 mL/min).

Dosage adjustment of Zavicefta is recommended in patients with moderate and severe renal impairment and end-stage renal disease. Table 2 shows the recommended dose adjustments for patients with estimated CrCL £ 50 mL/min. For patients with changing renal function, CrCl should be monitored at least daily and the dosage of Zavicefta adjusted accordingly. (see sections 4.4 Special warnings and precautions for use, Use in renal impairment, 5.1 Clinical trials and 5.2 Pharmacokinetic properties, Renal impairment).

Table 2: Recommended doses for patients with renal impairment[1]

Estimated CrCL (mL/min)	Dose regimen[2]	Frequency	Infusion time
31-50	1000 mg/250 mg	Every 8 hours	2 hours
16-30	750 mg/187.5 mg	Every 12 hours	2 hours
6-15	750 mg/187.5 mg	Every 24 hours	2 hours
ESRD including on haemodialysis[3]	750 mg/187.5 mg	Every 48 hours	2 hours

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

[2] Dose recommendations are based on pharmacokinetic modelling.

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

Hepatic impairment

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

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.

Elderly

No dosage adjustment is required in elderly patients (see section 5.2 Pharmacokinetic properties).

Paediatric population

Safety and efficacy in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

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

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 pale yellow solution and free of particles.

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

1. Introduce the syringe needle through the vial closure and inject 10 mL of sterile water for injections.

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

3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.

4. Transfer the entire contents (approximately 12.0 mL) of the resultant solution to an infusion bag immediately. Reduced doses may be achieved by transfer of an appropriate volume of the resultant solution to an infusion bag, based upon ceftazidime and avibactam content of 167.3 mg/mL and 41.8 mg/mL, respectively. A dose of 1000 mg/250 mg or 750 mg/187.5 mg is achieved with 6.0 mL or 4.5 mL aliquots, respectively.

Note: To preserve product sterility, it is important that the gas relief needle is not inserted through the vial closure before the product is dissolved.

Vials of ceftazidime/avibactam powder should be reconstituted with 10 mL of sterile water for injections, followed by shaking until the content dissolves.

An infusion bag may contain any of the following:

sodium chloride 9 mg/mL (0.9%)

dextrose 50 mg/mL (5%)

sodium chloride 4.5 mg/mL and dextrose 25 mg/mL (0.45% sodium chloride and 2.5% dextrose)

Lactated Ringer's solution.

A 100 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.

Product is for single use in one patient only. Discard any residue.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Hypersensitivity to any cephalosporin antibacterial agent.

Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of b-lactam antibacterial agent (e.g., penicillins, monobactams or carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 Contraindications and 4.8 (Adverse effects (undesirable effects)). In case of 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 hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of b-lactam antibacterial agent. Caution should be used if ceftazidime/avibactam is given to patients with a history of non-severe hypersensitivity to penicillins, monobactams or carbapenems.

Clostridium difficile-associated diarrhoea

Clostridium difficile-associated diarrhoea has been reported with ceftazidime/avibactam, and can range in severity from mild to life-threatening. This diagnosis should be considered in patients who present with diarrhoea during or subsequent to the administration of Zavicefta (see section 4.8 Adverse effects (undesirable effects)). Discontinuation of therapy with Zavicefta and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Nephrotoxicity

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

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

Ceftazidime/avibactam 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 drug induced immune haemolytic anaemia (see section 4.8 Adverse effects (undesirable effects)). While DAGT seroconversion in patients receiving Zavicefta was very common in clinical studies (the estimated range of seroconversion across Phase 3 studies was 3.2% to 20.8% in patients with a negative Coombs test at baseline and at least one follow-up test), there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. 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.

Spectrum of activity of ceftazidime/avibactam

Ceftazidime has little or no activity against the majority of Gram-positive organisms and anaerobes (see sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties). Additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of avibactam includes many of the enzymes that inactivate ceftazidime, including Ambler class A b-lactamases and class C b-lactamases. Avibactam does not inhibit class B enzymes (metallo-b-lactamases) and is not able to inhibit many of the class D enzymes (see section 5.1 Pharmacodynamic properties).

Non-susceptible organisms

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

Controlled sodium diet

Each vial contains a total of 6.44 mmol of sodium (approximately 148 mg). This should be considered when administering Zavicefta to patients who are on a controlled sodium diet.

Use in renal impairment

Ceftazidime and avibactam are eliminated via the kidneys, therefore, the dose should be reduced according to the degree of renal impairment (see section 4.2 Dose and method of administration). Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment.

In patients with renal impairment, close monitoring of estimated creatinine clearance is advised. In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection (see section 5.1 Clinical trials and 5.2 Pharmacokinetic properties, Renal impaiment.

Use in the elderly

No dosage adjustment is required in elderly patients (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Paediatric use

The safety and efficacy of Zavicefta in paediatric patients (< 18 years of age) have not been established.

Effects on laboratory tests

Ceftazidime may interfere with copper reduction methods (Benedict's, Fehling's, Clinitest) for detection of glycosuria leading to false positive results. Ceftazidime does not interfere with enzyme-based tests for glycosuria.

4.5 Interaction with other medicines and other forms of interactions

In vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake of avibactam from the blood compartment and therefore affect 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. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-administration of avibactam with probenecid is not recommended.

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

Clinical data have demonstrated that there is no interaction between ceftazidime and avibactam, and between ceftazidime/avibactam and metronidazole.

Other types of interaction

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g., furosemide) may adversely affect renal function (see section 4.4 Special warnings and precautions for use).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but due to the possibility of antagonism *in vivo* this drug combination should be avoided.

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effects of ceftazidime/avibactam on fertility in humans have not been studied. No data are available on animal studies with ceftazidime. Animal studies with avibactam do not indicate harmful effects with respect to male fertility. Studies in female rats showed a dose-related increase in pre-and post-implantation losses and smaller live litter size at ^{3} 500 mg/kg/day (^{3} 3 times the human therapeutic exposure at 500 mg three times a day, based on AUC).

Use in pregnancy - Pregnancy Category B3.

Ceftazidime

The safety of ceftazidime in pregnancy has not been established, although animal studies have not produced evidence of embryopathic or teratogenic effects attributable to ceftazidime.

Avibactam (Pregnancy Category B3)

Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects.

In pregnant rabbits administered avibactam at 300 and 1000 mg/kg/day (5-21 times the human therapeutic exposure based on AUC), there was a dose-related lower mean fetal weight and delayed ossification, associated with maternal toxicity (decreased food consumption and body weight gain). Plasma exposure levels at maternal and fetal NOAEL (100 mg/kg/day) indicate low margins of safety (1.5 times the human therapeutic exposure based on AUC).

In the rat, no adverse effects were observed on embryofetal development at up to 1000 mg/kg/day (6 times the human therapeutic exposure based on AUC). Following administration of avibactam throughout pregnancy and lactation in the rat, there was no effect on pup survival, growth or development, however there was an increase in incidence of dilation of the renal pelvis and ureters in less than 10% of the rat pups at maternal exposures ≥ 450 mg/kg/day (greater than or equal to approximately 3 times the human therapeutic exposures based on AUC). Ceftazidime/avibactam should only be used during pregnancy if the potential benefit outweighs the possible risk.

Use in lactation

Ceftazidime is excreted in human milk in small quantities.

It is unknown whether avibactam is excreted in human milk. Avibactam was excreted in rat milk (~20% of plasma C_{max}), and very low levels were detected in pup plasma (<0.03% of nonclinical maternal plasma C_{max}) as a result of exposure from milk.

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 following administration of Zavicefta (see section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

In seven Phase 2 and Phase 3 clinical trials, 2024 adult patients were treated with Zavicefta. The table below lists the adverse events (regardless of causality) occurring in ≥ 1% of patients treated with Zavicefta with or without metronidazole or comparator from Phase 2 and Phase 3 clinical trials.

Table 3: Adverse events (regardless of causality) reported by ³ 1% patients up to the last visit

	CAZ-AVI or CAZ-AVI+MTZ (N = 2024)	Comparator (N=2026)
Any AE	**996 (49.2)**	**965 (47.6)**
Infections and Infestations		
Pneumonia	21 (1.0)	26 (1.3)
Urinary tract infection	21 (1.0)	23 (1.1)
Blood and lymphatic system disorders		
Anaemia	46 (2.3)	38 (1.9)
Metabolism and nutrition disorders		
Hypokalaemia	57 (2.8)	45(2.2)
Psychiatric disorders		
Anxiety	23 (1.1)	18 (0.9)
Insomnia	25 (1.2)	35 (1.7)
Nervous systems disorders		
Headache	83 (4.1)	97 (4.8)
Dizziness	21 (1.0)	14 (0.7)
Cardiac disorders		
Tachycardia	20 (1.0)	13 (0.6)
Vascular disorders		
Hypotension	26 (1.3)	25 (1.2)
Hypertension	47 (2.3)	56 (2.8)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	20 (1.0)	18 (0.9)
Dyspnoea	20 (1.0)	18 (0.9)
Cough	30 (1.5)	29 (1.4)
Gastrointestinal disorders		
Diarrhoea	150 (7.4)	126 (6.2)
Constipation	62 (3.1)	66 (3.3)
Abdominal pain	39 (1.9)	30 (1.5)
Lower Abdominal pain	22 (1.1)	13 (0.6)
Nausea	102 (5.0)	64 (3.2)
Vomiting	78 (3.9)	50 (2.5)
Skin subcutaneous tissue disorders		
Rash	20 (1.0)	27 (1.3)
Musculoskeletal and connective tissue disorders		
Back pain	20 (1.0)	13 (0.6)

	CAZ-AVI or CAZ-AVI+MTZ (N = 2024)	**Comparator (N=2026)**
General disorders and administration site conditions		
Pyrexia	65 (3.2)	71 (3.5)
Asthenia	20 (1.0)	15 (0.7)
Oedema peripheral	36 (1.8)	26 (1.3)
Investigations		
Alanine aminotransferase increased	35 (1.7)	43 (2.1)
Aspartate aminotransferase increased	37 (1.8)	41 (2.0)

CAZ-AVI = ceftazidime-avibactam; MTZ = metronidazole; Comparator = meropenem , doripenem or best available therapy.

The most common adverse reactions occurring in ³ 5% of patients treated with Zavicefta were Coombs direct test positive, nausea, and diarrhoea. Nausea and diarrhoea were usually mild or moderate in intensity. No clinically significant differences were observed in the safety profile across indications.

The following adverse reactions have been reported with ceftazidime alone and/or identified during the Phase 2 and Phase 3 trials with Zavicefta. Adverse reactions are classified according to frequency as defined in the table below and System Organ Class. Frequency categories are derived from adverse reactions and/or potentially clinically significant laboratory abnormalities.

Table 4: Frequency of adverse reactions by system organ class

System Organ Class	**Very common (³ 10%)**	**Common (³ 1% and <10%)**	**Uncommon(³ 0 .1% and <1%)**	**Very rare (³ 0.01% and <0.1%)**	**Unknown (cannot be estimated from available data)**
Infections and infestations		Candidiasis (including vulvovaginal candidiasis and oral candidiasis)	Clostridium difficile colitis Pseudo-membranous colitis		
Blood and lymphatic system disorders	Coombs direct test positive	Eosinophilia Thrombocytosis Thrombocytopenia	Neutropenia Leukopenia Lymphocytosis		Agranulocytosis Haemolytic anaemia
Immune system disorders					Anaphylactic reaction
Nervous system disorders		Headache Dizziness	Paraesthesia		
Gastrointestinal disorders		Diarrhoea Abdominal pain Nausea Vomiting	Dysgeusia		

System Organ Class	Very common (³ 10%)	Common (³ 1% and <10%)	Uncommon(³ 0 .1% and <1%)	Very rare (³ 0.01% and <0.1%)	Unknown (cannot be estimated from available data)
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Gamma-glutamyltransferase increased Blood lactate dehydrogenase increased			Jaundice
Skin and subcutaneous tissue disorders		Rash maculo-papular Urticaria Pruritus			Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubulo-interstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosisv Infusion site phlebitis Pyrexia			

Reporting of suspected adverse effects

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. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdose with ceftazidime/avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis. During a 4-hour haemodialysis period, 55% of the avibactam dose was removed.

For advice on the management of overdose please contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOKINETIC 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 binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. Avibactam is a non b-lactam, b-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 b-lactamases and some class D enzymes, including extended-spectrum b-lactamases (ESBLs), KPC and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes (metallo-b-lactamases) and is not able to inhibit many class D enzymes.

Resistance

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, and b-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyse ceftazidime.

Antibacterial activity in combination with other antibacterial agents

No synergy or antagonism was demonstrated in *in vitro* drug combination studies with ceftazidime/avibactam and metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin and tigecycline.

Susceptibility testing breakpoints

Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ceftazidime/avibactam are as follows:

Organisms	**Susceptible**	**Resistant**
Enterobacteriaceae	£8 mg/L	>8 mg/L
P. aeruginosa	£8 mg/L	>8 mg/L

Clinical efficacy against specific pathogens

As detailed in the clinical studies discussed below, efficacy has been demonstrated against the following pathogens that were susceptible to ceftazidime/avibactam *in vitro*.

Complicated intra-abdominal infections

Gram-negative micro-organisms

- *Citrobacter freundii (C. freundii)*
- *Enterobacter cloacae (E. cloacae)*
- *Escherichia coli (E.coli)*
- *Klebsiella oxytoca (K. oxytoca)*
- *Klebsiella pneumoniae (K. pneumoniae)*
- *Pseudomonas aeruginosa (P. aeruginosa).*

Complicated urinary-tract infections

Gram-negative micro-organisms

- *E. coli*
- *K. pneumoniae*
- *Proteus mirabilis (P. mirabilis)*
- *E. cloacae*
- *P. aeruginosa.*

Hospital-acquired pneumonia including ventilator-associated pneumonia

Gram-negative micro-organisms

- *E. cloacae*
- *E. coli*
- *K. pneumoniae*
- *P. mirabilis*
- *Serratia marcescens (S. marcescens)*
- *P. aeruginosa.*

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to ceftazidime/avibactam in the absence of acquired mechanisms of resistance.

Gram-negative micro-organisms

- *Citrobacter koseri (C. koseri)*
- *Enterobacter aerogenes (E. aerogenes)*
- *Morganella morganii (M. morganii)*
- *Proteus vulgaris (P. vulgaris)*
- *Providencia rettgeri (P. rettgeri).*

In-vitro data indicate that the following species are not susceptible to ceftazidime/avibactam.

- *Staphylococcus aureus* (methicillin-susceptible and methicillin-reistant)
- Anaerobes
- *Enterococcus* spp.
- *Stenotrophomonas maltophilia*
- *Acinetobacter* spp.

Australian antibiotic resistance prevalence data

A surveillance study conducted in 2016 examined the susceptibility of ceftazidime/avibatam against clinical isolates collected from hospitalised patients. The *in vitro* data for clinical isolates are summarised in the table below. All isolates were obtained from specimens collected from patients with documented IAI, UTI, skin and skin structure infections (SSTI), blood cultures, or lower respiratory tract infections (LRTI). Only one strain per patient infection episode was included in the surveillance programme. Susceptiblity testing methods according to *Clinical Laboratory Standards Institute* (CLSI) (M2-09) were used and where applicable, susceptibility interpretive criteria applied were CLSI M100-S27 (2017).

Table 5: Summary of ceftazidime/avibactam (CAZ/AVI) activity tested against susceptible Gram negative clinical isolates from Australian tertiary hospitals from January to December 2016

Organism / subset	No. of isolates	MIC50 (mg/L)	MIC90 (mg/L)
Haemophilus. influenzae	39	£0.03	0.12
b lactamase-negative	31	£0.03	0.12
b lactamase-positive	8	--	--
Haemophilus parainfluenzae	2	--	--
Moraxella. catarrhalis	6	--	--
b-lactamase-positive	4	--	--
Enterobacteriaceae	522	0.12	0.5
E. coli	150	0.12	0.25
ESBL (molecular)[1]	17	0.12	0.25
ESBL (screen negative)[2]	120	0.06	0.12
meropenem- susceptible (MIC of £ 1mg/L)	149	0.12	0.25
meropenem non-susceptible (MIC of ³ 2 mg/L)	1	--	--
Klebsiella spp.[3]	174	0.12	0.5
ESBL (molecular)[1]	16	0.25	>128

Organism / subset	No. of isolates	MIC50 (mg/L)	MIC90 (mg/L)
ESBL (screen negative)[2]	149	0.12	0.25
K. pneumoniae	148	0.12	0.5
ESBL (molecular)[1]	16	0.25	>128
ESBL (screen negative)[2]	127	0.12	0.5
Meropenem-susceptible (MIC £ 1 mg/mL)	145	0.12	0.5
Meropenem non-susceptible (MIC ³ 2 mg/mL)	3	--	--
K. oxytoca	24	0.12	0.25
ESBL (screen negative)[2]	20	0.12	0.12
M. morganii	10	0.06	0.25
***Citrobacter* spp.**	63	0.12	>128
C. freundii	38	0.25	>128
C. koseri	18	0.12	0.5
***Enterobacter* spp[4].**	62	0.25	0.5
CAZ-susceptible (MIC £ 4 mg/mL)	37	0.12	0.25
CAZ non-susceptible (MIC ³ 8 mg/mL)	25	0.5	1
E. aerogenes	22	0.25	0.5
CAZ-susceptible (MIC £ 4 mg/mL)	11	0.12	0.25
CAZ non-susceptible (MIC ³ 8 mg/mL)	11	0.25	0.5
E. cloacae	34	0.25	0.5
CAZ-susceptible (MIC £ 4 mg/mL)	21	0.25	0.25
CAZ-non-susceptible (MIC ³ 8 mg/mL)	13	0.5	1
S. marcescens	7	--	--
P. mirabilis	23	0.03	0.06
ESBL (molecular)[2]	1	--	--
ESBL (screen negative)[3]	21	0.03	0.06
P. vulgaris	19	0.03	0.12
***Providencia* spp.[5]**	12	0.03	0.12

Organism / subset	No. of isolates	MIC50 (mg/L)	MIC90 (mg/L)
P. aeruginosa	146	2	4
Meropenem-susceptible (MIC £ 2 mg/mL)	122	2	4
Meropenem-non-susceptible (MIC ³ 4 mg/mL)	24	4	16
CAZ-susceptible (MIC £ 8 mg/mL)	127	2	4
CAZ-non-susceptible (MIC ³ 16 mg/mL)	19	4	32

Abbreviations: CAZ-AVI = ceftazidime-avibactam, N= number of isolates tested, MIC$_{50}$ and MIC values not calculated for n<10.

1. ESBL (molecular) = isolates which a *bla* gene encoding an ESBL detected by PCR and may also contain genes encoding other b-lactamases.

2. ESBL (screen negative) = any isolate with ceftazidime, aztreonam, MIC values £ 1 mg/L.

3. *Klebsiella* spp., *Oxytoca* (n=24), *pneumoniae* (n=148); *variicola* (n= 2).

4. *Enterobacter* spp., *Aerogenes* (n = 22)*; asburiae* (n = 5), *cloacae* (n = 34), *kobei (*n -= 1).

5. *Providencia* spp., *Rettgeri* (n=8); *stuartii* (n=4).

Clinical trials

Complicated intra-abdominal infections (cIAI)

In two identical randomised, multi-centre, multinational, double-blind studies (RECLAIM 1 and RECLAIM 2), a total of 1058 adults with cIAI were randomised to receive treatment comparing Zavicefta (2000 mg of CAZ and 500 mg of AVI) administered intravenously over 120 minutes every 8 hours plus metronidazole (500 mg) to meropenem (1000 mg) administered intravenously over 30 minutes. Treatment duration was 5 to 14 days. cIAI (defined as infections that require surgical intervention and extend beyond the hollow viscus into the intraperitoneal space) included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis.

The modified intent-to-treat (MITT) population included all patients who met the disease definition of cIAI and received at least 1 dose of the study drug. The clinically evaluable (CE) population included patients who had an appropriate diagnosis of cIAI and excluded patients with a bacterial species typically not expected to respond to both study drugs (i.e. *Acinetobacter baumannii* or *Stenotrophomonas* spp) and/or who had an important protocol deviation impacting the assessment of efficacy.

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

Table 6: Clinical cure rate at TOC (RECLAIM MITT and CE analysis sets)

Analysis set	**Number (%) of patients**		
Response	**CAZ/AVI + MTZ**	**Meropenem**	**Difference (%) 95% CI**
MITT	(N=520)	(N=523)	
Clinical cure	429 (82.5)	444 (84.9)	-2.4 (-6.90, 2.10)
CE	(N=410)	(N=416)	
Clinical cure	376 (91.7)	385 (92.5)	-0.8 (-4.61, 2.89)

Clinical cure rates at TOC by pathogen in the microbiologically modified intent-to-treat (mMITT) population for Gram-negative aerobes are shown in the table below.

Table 7: Clinical cure rate at TOC by common (combined frequency of ³ 10) Gram-negative baseline pathogen (RECLAIM mMITT analysis set)

Number of patients						
	CAZ/AVI + MTZ (N=413)			**Meropenem (N=410)**		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**N**
Enterobacteriaceae	81.4	272	334	86.4	305	353
C. freundii complex	77.8	14	18	75.0	9	12
E. aerogenes	80.0	4	5	100	5	5
E. cloacae	84.6	11	13	84.2	16	19
E. coli	80.4	218	271	87.0	248	285
K. oxytoca	77.8	14	18	80.0	12	15
K. pneumoniae	78.4	40	51	75.5	37	49
P. mirabilis	62.5	5	8	77.8	7	9
P. aeruginosa	85.7	30	35	94.4	34	36

A further 432 adults with complicated intra-abdominal infections were randomised and received treatment in a multi-centre, double-blind study (RECLAIM 3) conducted in 3 Asian countries (China, Republic of Korea and Vietnam). The patient population and key aspects of the study design were identical to RECLAIM apart from the primary efficacy endpoint of clinical response at the TOC visit being solely in the CE population (see table below).

Table 8:Clinical cure rates at TOC (RECLAIM 3 CE at TOC analysis set)

	Number (%) of patients		
	CAZ/AVI + MTZ	**Meropenem**	**Difference (%) 95% CI**
	(N=177)	(N=184)	
Clinical cure	166 (93.8)	173 (94.0)	-0.2 (-5.53, 4.97)

Clinical cure rates at TOC by pathogen in the microbiologically modified intent-to-treat (mMITT) population for Gram-negative aerobes are shown in the table below.

Table 9: Clinical cure rates at TOC by common (combined frequency of ^{3} 7) Gram-negative baseline pathogen (RECLAIM 3 mMITT analysis set)

Number of patients						
	CAZ/AVI + MTZ (N=143)			**Meropenem (N=152)**		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**N**
Enterobacteriaceae	80.9	93	115	92.7	115	124
C. freundii complex	62.5	5	8		0	0
E. cloacae	100	5	5	66.7	2	3
E. coli	83.3	70	84	94.4	84	89
K. oxytoca	100	5	5	100	5	5
K. pneumoniae	82.1	23	28	88.6	31	35
P. mirabilis	66.7	2	3	100	5	5
P. aeruginosa	82.4	14	17	85.0	17	20

In Phase 3 cIAI clinical trials, death occurred in 2.1% (18/857) of patients who received Zavicefta and metronidazole and in 1.4% (12/863) of patients who received meropenem. Among a subgroup with baseline CrCL 30 to 50 mL/min, death occurred in 16.7% (9/54) of patients who received Zavicefta and metronidazole and 6.8% (4/59) of patients who received meropenem. Patients with CrCL 30 to 50 mL/min received a lower dose of Zavicefta than is currently recommended for patients in this sub-group.

In a phase 3 cIAI clinical trial, clinical cure rates were lower in a subgroup of patients with baseline CrCl of 30 to 50 mL/min compared to those with CrCl > 50 mL/min. The reduction in clinical cure rates was more marked in patients treated with Zavicefta plus metronidazole compared to meropenem-treated patients. The decreased clinical response was not observed for patients with moderate renal impairment at baseline (CrCl of 30 to 50 mL/min) in the Phase 3 cUTI trials or the Phase 3 HAP/VAP trial. See sections 4.2 Dose and method of aministration, 4.4 Special warnings and precautions for use, Use in renal impairment, 5.2 Pharmacokinetic properties, Renal impairment).

Complicated urinary tract infections (cUTI)

A total of 1020 adults with documented cUTI (737 with acute pyelonephritis and 283 with cUTI without acute pyelonephritis) were randomised and received treatment in a phase III multicentre, double-blind, comparative study. cUTI included acute pyelonephritis and complicated lower urinary tract infections. Treatment was with either ceftazidime/avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or doripenem 500 mg IV over 60 mins every 8 hours. There was an optional switch to oral therapy for patients who had clinical improvement as defined in the study protocol after a minimum of 5 days IV treatment. Total duration of antibiotic therapy (IV plus oral) was 10 days (optionally up to 14 if bacteraemic). The mMITT population included all patients with a confirmed cUTI diagnosis, received at least 1 dose of study treatment and had a study-qualifying pre-treatment urine culture containing 105 CFU/mL of a Gram-negative pathogen and no more than 2 species of microorganisms. Any patient with a Gram-positive pathogen, or a bacterial species not expected to respond to both study drugs was excluded. Patients with CrCl < 30 mL/min were excluded.

The primary efficacy endpoint was per-patient microbiological response at the TOC visit in the mMITT analysis set.

Table 10: Favourable per-patient microbiological response rate at TOC (RECAPTURE mMITT analysis set

		CAZ/AVI (N=393)	Doripenem (N=417)	Difference (%) (95% CI)
Per patient microbiological response	Favourable	304 (77.4)	296 (71.0)	6.4 (0.33, 12.36)

Favourable microbiological response rates at TOC by pathogen in the mMITT population are shown in the table below.

Table 11: Favourable per-pathogen microbiological response rate at TOC by common (combined frequency of ^{3} 10) baseline pathogen (RECAPTURE mMITT)

Number of patients						
	CAZ/AVI (N=393)			Doripenem (N=417)		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**n**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacteriaceae	78.3	299	382	70.6	281	398
E. cloacae	54.5	6	11	69.2	9	13
E. coli	78.4	229	292	71.9	220	306
K. pneumoniae	75.0	33	44	62.5	35	56
P. mirabilis	94.1	16	17	69.2	9	13
P. aeruginosa	66.7	12	18	75.0	15	20

Hospital-acquired pneumonia (HAP)

In a phase III double-blind, comparative study, a total of 808 adults with nosocomial pneumonia (280/808, 34.7% with VAP and 40/808 (5.0%) were bacteraemic at baseline) were randomised to receive treatment of ceftazidime/avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or meropenem 1g IV over 30 mins every 8 hours. Treatment duration was 7 to 14 days. Nosocomial pneumonia was defined as an onset of relevant signs and symptoms ^{3} 48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility, and a new or worsening infiltrate on chest X-ray obtained within 48 hours prior to randomisation. Patients with infections only due to Gram-positive organisms were excluded from the trial, when this could be determined before enrollment. Following randomisation, patients in both treatment groups could receive empiric open-label linezolid or vancomycin to cover for Gram-positive pathogens while awaiting culture results. Treatment with Gram-positive coverage continued in patients with Gram-positive pathogens.

The clinically modified intent-to-treat (cMITT) population included patients who met the minimum disease criteria, received at least 1 dose of study treatment and who had properly obtained baseline respiratory or blood cultures demonstrating Gram-negative pathogens excluding patients with monomicrobial Gram-negative infections with species not expected to respond to both study drugs (e.g., *Acinetobacter* species or *Stenotrophomonas* species). The cMITT also included patients in whom no aetiologic pathogens were identified from respiratory or blood cultures at baseline. The CE at TOC analyses set was the clinically evaluable subset of the cMITT.

The primary efficacy endpoint was the clinical response at the TOC visit in the co-primary populations of the cMITT and CE at TOC. See table below.

Table 12: Clinical cure rates at TOC (REPROVE cMITT and CE at TOC analysis sets)

Number (%) of patients				
Analysis set	**Response**	**CAZ/AVI**	**Meropenem**	**Difference (%) 95% CI**
cMITT		(N=356)	(N=370)	
	Clinical cure	245 (68.8)	270 (73.0)	-4.2 (-10.76, 2.46)
CE at TOC		(N=257)	(N=270)	
	Clinical cure	199 (77.4)	211 (78.1)	-0.7 (-7.86, 6.39)

All-cause mortality rates at Day 28 (cMITT) was 8.4% (30/356) and 7.3% (27/370) ceftazidime/avibactam and meropenem treated patients, respectively.

Clinical cure rate and favourable microbiological response rate at TOC by pathogen in mMITT for Gram-negative aerobes are shown in Tables 13 and 14.

Table 13: Clinical cure rate at TOC by common (combined frequency of ³ 10) Gram-negative baseline pathogen (REPROVE mMITT)

Number of patients						
	CAZ/AVI (N=171)			**Meropenem (N=184)**		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacteriaceae	73.6	89	121	75.4	104	138
E. aerogenes	62.5	5	8	50.0	4	8
E. cloacae	92.3	24	26	54.5	12	22
E. coli	64.7	11	17	75.0	15	20
K. pneumoniae	72.9	43	59	77.5	55	71
P. mirabilis	85.7	12	14	75.0	9	12
Serratia marcescens	73.3	11	15	92.3	12	13
P. aeruginosa	60.3	35	58	74.5	35	47
H. influenzae	81.3	13	16	80.0	20	25

Table 14: Per-pathogen microbiological response at TOC by common (combined frequency of ³ 10) Gram-negative baseline pathogen (REPROVE mMITT)

Number of patients						
	CAZ/AVI (N=171)			**Meropenem (N=184)**		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**N**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacteriaceae						
E. aerogenes	*62.5*	*5*	*8*	*62.5*	*5*	*8*
E. cloacae	*80.8*	*21*	*26*	*59.1*	*13*	*22*
E. coli	*76.5*	*13*	*17*	*80.0*	*16*	*20*
K. pneumoniae	*62.7*	*37*	*59*	*74.6*	*53*	*71*
P. mirabilis	*78.6*	*11*	*14*	*66.7*	*8*	*12*
S. marcescens	*66.7*	*10*	*15*	*61.5*	*8*	*13*
P. aeruginosa	*37.9*	*22*	*58*	*38.3*	*18*	*47*
H. influenzae	*87.5*	*14*	*16*	*92.0*	*23*	*25*

Limitations of clinical trial data

Patients with evidence of significant immunocompromise were excluded from the Phase 3 clinical trials.

5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were about 22 L and 18 L, respectively in healthy adults following multiple doses of 2000 mg/500 mg ceftazidime/avibactam infused over 2 hours every 8 hours. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% of those in plasma. The concentration time profiles are similar for ELF and plasma.

Penetration of ceftazidime into the intact blood-brain barrier is poor. Ceftazidime 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 AUC, respectively. Ceftazidime crosses the placenta readily, and is excreted in the breast milk.

Metabolism

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

Excretion

The terminal half-life ($t_{½}$) of both ceftazidime and avibactam is about 2 h after intravenous administration. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80-90% of the dose is recovered in the urine within 24 h. 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 avibactam dose is recovered in the urine, 95% within 12 h. 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 2000 mg) for a single intravenous administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple intravenous infusions of 2000 mg/500 mg of ceftazidime/avibactam administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Pharmacokinetic/pharmacodynamic relationship(s)

The antimicrobial activity of ceftazidime against specific pathogens has been shown to best correlate with the percent time of free-drug concentration above the ceftazidime/avibactam minimum inhibitory concentration over the dose interval (%*f*T >MIC of ceftazidime/avibactam). For avibactam the PK-PD index is the percent time of the free drug concentration above a threshold concentration over the dose interval (% *f*T >C_T).

Renal impairment

Ceftazidime is eliminated almost solely by the kidneys; its serum half-life is significantly prolonged in patients with impaired renal function. The clearance of avibactam was significantly decreased in subjects with mild (CrCl > 50 to 80 mL/min, n = 6), moderate (CrCl 30 to 50 mL/min, n = 6), and severe (£ CrCl 30 mL/min, not requiring haemodialysis; n = 6) renal impairment compared to healthy subjects with normal renal function (CrCl ³ 80 mL/min, n = 6) following administration of a single 100 mg intravenous dose of avibactam. The slower clearance resulted in increases in systemic exposure (AUC) of avibactam of 2.6-fold, 3.8-fold and 7-fold in subjects with mild, moderate and severe renal impairment, respectively.

A single 100 mg dose of avibactam was administered to subjects with ESRD (n = 6) either 1 hour before or after haemodialysis. The avibactam AUC following the post-haemodialysis infusion was 19.5-fold the AUC of healthy subjects with normal renal function. Avibactam was extensively removed by haemodialysis, with an extraction coefficient of 0.77 and a mean haemodialysis clearance of 9.0 L/h. Approximately 55% of the avibactam dose was removed during a 4-hour haemodialysis session.

Dosage adjustment of Zavicefta is recommended in patients with moderate and severe renal impairment and end-stage renal disease. Population PK models for ceftazidime and avibactam were used to conduct simulations for patients with impaired renal function. Simulations demonstrated that the recommended dose adjustments provide comparable exposures of ceftazidime and avibactam in patients with moderate and severe renal impairment and end-stage renal disease to those in patients with normal renal function or mild renal impairment. For patients with changing renal function, CrCl should be monitored at least daily and the dose of Zavicefta adjusted accordingly (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precuations for use, Use in renal impairment).

Hepatic impairment

Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 200 mg intravenously 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 active substance is not expected to be significantly altered by hepatic impairment.

Use in the elderly

Reduced clearance of ceftazidime was observed in elderly patients, which was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life of ceftazidime ranged from 3.5 to 4 hours following intravenous bolus dosing with 2000 mg every 12 hours in elderly patients aged 80 years or older.

Following a single intravenous 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.

Gender and race

The pharmacokinetics of ceftazidime/avibactam is not significantly affected by gender or race.

5.3 Preclinical safety data

Genotoxicity

For ceftazidime, a mouse micronucleus test and an Ames test were both negative for mutagenic effects. In genotoxicity assays with avibactam, there was no induction of gene mutation in the *in vitro* bacterial reverse mutation tests, nor were there any indications of genotoxicity in an *in vitro* micronucleus test in mouse lymphoma cells. In cultured human lymphocytes, statistically significant increases in chromosomal aberrations were observed under a single treatment condition (44h harvest time, -S9). As these findings were not replicated in an independent study, the results are considered to be of limited biological relevance. When administered up to the limit dose of 2 g/kg IV, avibactam was negative in a rat *in vivo* micronucleus assay. No genetic toxicology studies have been conducted on ceftazidime-avibactam.

Carcinogenicity

Carcinogenicity studies have not been conducted with ceftazidime-avibactam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium carbonate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Dry powder

3 years.

After reconstitution

The reconstituted vial should be used immediately.

The chemical and physical in-use stabilityof the reconstituted product has been demonstrated for up to 24 hours 2 - 8°C followed by up to 12 hours at not more than 25°C.

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 12 hours at not more than 25°C or 24 hours at 2 - 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from light.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3 Shelf life.

6.5 Nature and contents of container

20 mL glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap.

The medicinal product is supplied in packs of 10 vials.

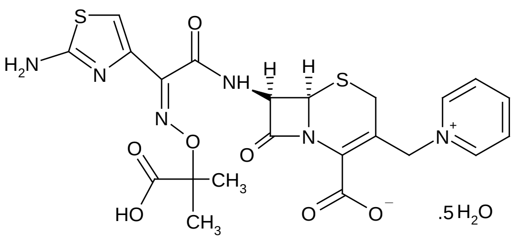
6.6 Special precautions for disposal

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

6.7 Physicochemical propperties

Chemical structure

Ceftazidime (as pentahydrate)

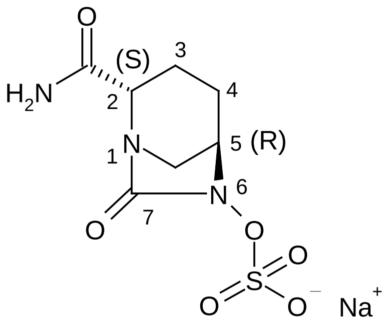


CAS number

78439-06-2.

Chemical structure

Avibactam (as sodium)



CAS number

1192491-61-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

22 February 2019.

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