▼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 THE 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).

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).

Zavicefta is indicated for the treatment of the following infections in infants and paediatric patients (≥ 3 months to < 18 years) (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.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zavicefta and other antibiotics, 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

Adult

The recommended dosage is one 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

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

Adults

Renal impairment

No dosage adjustment is required in patients with mild renal impairment (estimated creatinine clearance (CrCL) ≥ 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 Pharmacodynamic properties, Clinical trials and 5.2 Pharmacokinetic properties, Renal impairment).

Table 2: Recommended doses for adult 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.

Haemodialysis

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

Haemofiltration or peritoneal dialysis

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

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.

Elderly

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

Paediatric population

Safety and efficacy in infants < 3 months old have not been established. The recommended dosage and duration of treatment for infants and paediatric patients (≥ 3 months to < 18 years old) is summarised in the Table below. Dosage adjustment of Zavicefta in paediatric patients with renal impairment (2 years to < 18 years) are shown in Table 4 below.

Table 3: Dosage in paediatric patients (≥ 3 months to < 18 years old)

Type of infection	Age group[4]	Dosage of CAZ/AVI	Frequency	Infusion time	Duration of treatment
cIAI[1, 2] OR cUTI including pyelonephritis[2]	6 months to < 18 years	**50 mg/kg**/12.5 mg/kg **to a maximum of 2000 mg**/500 mg	Every 8 hours	2 hours	cIAI: 7 – 14 days[3] cUTI: 7 – 14 days[3]
	≥ 3 months to < 6 months	**40 mg/kg**/10 mg/kg	Every 8 hours	2 hours	

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

[1] Used in combination with metronidazole (MTZ) 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.

[4]. There is no clinical data in children from 3 months to 2 years for this indication. Recommended dosing for this age group is based on pharmacokinetic data.

Paediatric patients with renal impairment

Table 4: Recommended doses for paediatric patients (2 years to < 18 years old) with renal impairment[1]

Age Group	Estimated CrCL (mL/min)[1]	Dose of CAZ/AVI[2]	Frequency	Infusion time
2 years to < 18 years	31-50	**25 mg/kg**/6.25 mg/kg **to a maximum of 1000 mg**/250 mg	Every 8 hours	2 hours
	16-30	**18.75 mg**/kg/4.75 mg/kg **to a maximum of 750 mg**/187.5 mg	Every 12 hours	2 hours
	6-15		Every 24 hours	2 hours
	ESRD including on haemodialysis[3]		Every 48 hours	2 hours

Abbreviations: CAZ/AVI =ceftazidime/avibactam.

[1] CrCL estimated using the Schwartz bedside formula for paediatric patients (mL/min/1.73 m^2).

[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.

There is insufficient information to recommend a dosage regimen for paediatric patients less than 2 years of age with a creatinine clearance of < 50 mL/min/1.73 m^2.

There is insufficient clinical data to make specific dosage adjustment recommendations for children < 18 years undergoing haemofiltration or peritoneal dialysis.

Method of administration

Zavicefta is administered by intravenous infusion over 120 minutes. For instructions on reconstitution, dilution and preparation of infusion volume of the product before administration see information under the subsection heading, Reconstitution and Preparation of infusion volume later in this section.

Reconstitution

The powder must be reconstituted with water for injections and the resulting solution must then be immediately diluted prior to use.

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

The reconstitution time can be up to 4 minutes.

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

Doses may be prepared in an appropriately sized infusion bags or infusion syringes.

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

Refer to section 6.3 Shelf life for shelf life of the dry powder, reconstituted solution and the dilued solutions stored in infusion bags and infusion syringes.

Each vial is for single use only. Discard any residues.

Preparation of infusion volume

Zavicefta (ceftazidime/avibactam) is a combination product; each vial contains 2000 mg of ceftazidime and 500 mg of avibactam in a fixed 4:1 ratio. Dosage recommendations are based on the ceftazidime component only.

Instructions for preparing adult and paediatric doses for patients older than 12 months in INFUSION BAGS or in INFUSION SYRINGES

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 solution are provided later in this section (see Table 6).

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 (must contain **8-40 mg/mL** ceftazidime):
   a. Infusion bag: Further dilute the reconstituted solution by transferring an appropriately calculated volume of the reconstituted solution to an infusion bag containing any of the following: sodium chloride 9 mg/mL (0.9%) solution for injection, dextrose 50 mg/mL (5%) solution for injection or Lactated Ringer's solution.
   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.

Refer to the Table below.

Table 5: Preparation of Zavicefta for adult and paediatric doses for patients older than 12 months 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
2000 mg	Entire contents (approximately 12 mL)	50 mL to 250 mL	50 mL
1000 mg	6 mL	25 mL to 125 mL	25 mL to 50 mL
750 mg	4.5 mL	19 mL to 93 mL	19 mL to 50 mL
All other doses	Volume (mL) calculated based on dose required:	Volume (mL) will vary based on infusion bag size availability. Final infusion	Volume (mL) will vary based on infusion syringe size availability. Final

Zavicefta Dose (ceftazidime)[1]	Volume to withdraw from reconstituted vial	Final volume after dilution in infusion bag[2]	Final volume in infusion syringe
	Dose (mg ceftazidime) ÷ 167.3 mg/mL ceftazidime	solution must contain 8-40 mg/mL ceftazidime.	infusion solution must contain 8-40 mg/mL 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 room temperature (i.e., dilute 2000 mg dose of ceftazidime in 250 mL, 1000 mg dose of ceftazidime in 125 mL, 750 mg 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 room temperature.

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 a 20 mg/mL ceftazidime infusion solution. Alternative doses may be prepared, but the final solution must contain 8-40 mg/mL of ceftazidime.

1. Prepare the r**econstituted 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 of 20 mg/mL 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 6 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 utilised to estimate the approximate volume to verify the calculation.

Table 6: Preparation of the final Zavicefta solution (20 mg/mL 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

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)
	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.

4.3 Contraindications

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

Hypersensitivity to any cephalosporin antibacterial agent.

Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of β-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 β-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.

Clostridioides difficile-associated diarrhoea

Clostridioides 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 *Clostridioides 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.

Dermatological adverse events

Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life threatening or fatal, have been reported in patients taking beta-lactam antibiotics (see section 4.8 Adverse effects (undesirable effects)). When SCAR is suspected, Zavicefta should be discontinued immediately and an alternative treatment should be considered. See section 4.8 Adverse effects (undesirable effects).

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 β-lactamases and class C β-lactamases. Avibactam does not inhibit class B enzymes (metallo-β-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.

Development of drug-resistant bacteria

Prescribing Zavicefta in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria (see section 4.1. Therapeutic indications).

Controlled sodium diet

Each vial contains approximately 6.37 mmol of sodium per vial. This total is the combined sodium from avibactam sodium and the excipient sodium carbonate. This should be considered when administering Zavicefta to patients who are on a controlled sodium diet.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

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 impairment).

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 (< 3 months of age) have not been established.

There is a potential risk of overdosing, particularly for paediatric patients aged from 3 to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose (see sections 4.2 Dose and method of administration and 4.9 Overdose).

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 Interactions 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 ≥ 500 mg/kg/day (≥ 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 7: Adverse events (regardless of causality) reported by ≥ 1% adult 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		

	CAZ/AVI or CAZ/AVI+MTZ (N = 2024)	Comparator (N=2026)
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)
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 ≥ 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 8: Frequency of adverse reactions in adult patients by system organ class

System Organ Class	Very common (≥ 10%)	Common (≥ 1% and < 10%)	Uncommon (≥ 0.1% and < 1%)	Very rare (≥ 0.01% and < 0.1%)	Unknown (cannot be estimated from available data)
Infections and infestations		Candidiasis (including vulvovaginal candidiasis and oral candidiasis)	*Clostridioides 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 Kounis syndrome[+]
Nervous system disorders		Headache Dizziness	Paraesthesia		
Gastrointestinal disorders		Diarrhoea Abdominal pain Nausea Vomiting	Dysgeusia		
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Gamma-glutamyl transferase 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

System Organ Class	Very common (≥ 10%)	Common (≥ 1% and < 10%)	Uncommon (≥ 0.1% and < 1%)	Very rare (≥ 0.01% and < 0.1%)	Unknown (cannot be estimated from available data)
					Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders			Blood creatinine increased Blood urea increased Acute kidney injury	Tubulo-interstitial nephritis	
General disorders and administration site conditions		Infusion site thrombosis Infusion site phlebitis Pyrexia			

[+] Acute coronary syndrome associated with an allergic reaction.

Use in paediatrics

The safety assessment in paediatric patients is based on the safety data from two clinical trials in which 61 paediatric patients (aged from 3 years to less than 18 years) with cIAI and 67 patients with cUTI (aged from 3 months to less than 18 years) received Zavicefta. Hence, no adverse drug reactions were seen which are expected to be observed in less than 1 in 100 patients (i.e., frequency categories of uncommon, rare, very rare, and frequency unknown). The safety profile in children appears to mirror the safety profile in adults and uncommon, rare, and very rare adverse events seen in adults are likely to occur in children as paediatric usage of the drug increases.

Post-marketing experience

Nervous system disorders: Seizures, encephalopathy, myoclonus – frequency unknown.

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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 binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. 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 and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), KPC and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes (metallo-β-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 β-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

Susceptibility testing interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is recommended (*https://www.eucast.org/*).

EUCAST breakpoints are based on the dosages below. Alternative dosing regimens may result in equivalent exposure. The table should not be used as a guidance for dosing in clinical practice as dosages can vary widely by indication. It does not replace specific national, regional or local dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

The EUCAST Breakpoint Tables v. 14.0 2024 indicates that the standard dosage on which breakpoints are based is (2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours. For inhibition zone determination, the disks contain 10 micrograms ceftazidime and 4 micrograms avibactam.

The EUCAST breakpoints for ceftazidime-avibactam are listed in the following table:

EUCAST Susceptibility Interpretive Criteria for Ceftazidime-Avibactam				
	Minimal Inhibitory Concentration (mg/L of Ceftazidime)[a]		**Disk Diffusion Inhibition Zone (mm Diameter)**	
Pathogen	**S≤**	**R>**	**S≥**	**R<**
Enterobacterales (Enterobacteriaceae)	8	8	13	13
P. aeruginosa	8	8	17	17

Sources: EUCAST Clinical Breakpoint Table v. 14.0, 1 January, 2024.
S = Susceptible. R = Resistant.
[a]. For MIC determination, avibactam is present at a fixed concentration of 4 mg/L.

Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

Quality control ranges for EUCAST susceptibility breakpoints are listed in the following table.

Quality Control Ranges for Ceftazidime-Avibactam to be Used In Conjunction With EUCAST Susceptibility Test Interpretive Criteria		
	Minimal Inhibitory Concentration (mg/L of Ceftazidime)[a]	**Disk Diffusion Inhibition Zone (mm Diameter)**
Quality Control Strain		
Escherichia coli ATCC 25922	0.06-0.25	24-30
Pseudomonas aeruginosa ATCC 27853	0.5-4	21-27
Klebsiella pneumoniae ATCC 700603	0.25-2	18-24

Source: The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 14.0, 2024.
[a]. For MIC determination, avibactam is present at a fixed concentration of 4 mg/L.

Clinical efficacy against specific pathogens

This list is provided based on clinical efficacy and pharmacokinetic/pharmacodynamic data from clinical studies. The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. Efficacy has been demonstrated in clinical studies against the following pathogens, listed under each indication, 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 oxytocoa (K. oxytocoa)*
- *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-resistant)
- Anaerobes

- *Enterococcus spp.*
- *Stenotrophomonas maltophilia*
- *Acinetobacter spp.*

Australian antibiotic resistance prevalence data

A surveillance study conducted in 2016 examined the susceptibility of ceftazidime/avibactam 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. Susceptibility 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 9: 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	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Haemophilus. influenzae	39	≤ 0.03	0.12
β lactamase-negative	31	≤ 0.03	0.12
β lactamase-positive	8	--	--
Haemophilus parainfluenzae	2	--	--
Moraxella. catarrhalis	6	--	--
β-lactamase-positive	4	--	--
Enterobacterales (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 ≤ 1 mg/L)	149	0.12	0.25
Meropenem non-susceptible (MIC of ≥ 2 mg/L)	1	--	--
Klebsiella spp.[3]	174	0.12	0.5
ESBL (molecular)[1]	16	0.25	> 128
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 ≥ 2 mg/mL)	3	--	--
K. oxytocoa	24	0.12	0.25
ESBL (screen negative)[2]	20	0.12	0.12
M. morganii	10	0.06	0.25

Organism / subset	No. of isolates	MIC_{50} (mg/L)	MIC_{90} (mg/L)
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 ≥ 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 ≥ 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 ≥ 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
P. aeruginosa	146	2	4
Meropenem-susceptible (MIC ≤ 2 mg/mL)	122	2	4
Meropenem-non-susceptible (MIC ≥ 4 mg/mL)	24	4	16
CAZ-susceptible (MIC ≤ 8 mg/mL)	127	2	4
CAZ-non-susceptible (MIC ≥ 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 β-lactamases.

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

[3]. *Klebsiella* spp., *Oxytocoa* (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 10: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

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 11: Clinical cure rate at TOC by common (combined frequency of ≥ 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**
Enterobacterales (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. oxytocoa	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

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

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 12: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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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 13: Clinical cure rates at TOC by common (combined frequency of ≥ 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**
Enterobacterales (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. oxytocoa	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

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

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

administration, 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 3 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 14: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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

Table 15: Favourable per-pathogen microbiological response rate at TOC by common (combined frequency of ≥ 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**
Enterobacterales (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

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

Hospital-acquired pneumonia (HAP)

In a Phase 3 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 1 g 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 ≥ 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 16: 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)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

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 17 and 18.

Table 17: Clinical cure rate at TOC by common (combined frequency of ≥ 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**
Enterobacterales (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

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

Table 18: Per-pathogen microbiological response at TOC by common (combined frequency of ≥ 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**
Enterobacterales (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

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

Paediatric patients

Ceftazidime/avibactam has been evaluated in paediatric patients in two Phase 2 single-blind, randomised, comparative clinical studies, one in patients with cIAI and one in patients with cUTI. Patients aged 3 months to < 18 years were eligible for both studies, but in the cIAI study, the youngest patient was 3 years of age (median age: 11 years). Patients aged ≥ 3 months to < 1 year must have been born at term (defined as gestational age ≥ 37 weeks). Patients treated

with ceftazidime/avibactam in the cIAI trial also received metronidazole (administered per local label; suggested dose: 10 mg/kg every 8 hours, administered IV over 20 to 30 minutes). The primary objective in each study was to assess safety and tolerability of ceftazidime/avibactam or ceftazidime/avibactam plus metronidazole. Secondary objectives included assessment of PK and efficacy; efficacy was a descriptive endpoint in both studies.

cIAI

A total of 83 paediatric patients with cIAI were randomised (3:1) and received treatment with either CAZ/AVI plus metronidazole (n=61) (doses provided in Table 3), or meropenem (n=22), 20 mg/kg IV every 8 hours. After a minimum of 72 hours of IV treatment, there was an optional switch to oral therapy for patients who had clinical improvement, as defined in the study protocol. The total duration of antibiotic therapy (IV plus oral) was between 7 and 15 days. TOC assessments were performed 8 to 15 days after the last dose of study drug (IV or oral).

The majority of patients (87%) had appendiceal perforation or peri-appendiceal abscess (52/61, 85.2% CAZ/AVI plus metronidazole; 20/22, 90.9% meropenem). The CE population included patients who had a confirmed diagnosis of cIAI and received a minimum duration of IV study drug, and excluded patients who had a clinical response of indeterminate and/or an important protocol deviation impacting the assessment of efficacy. The microbiological intent-to treat (micro-ITT) population included 69 patients (50 CAZ/AVI plus metronidazole, 19 meropenem) who had at least one baseline intra-abdominal pathogen. Favourable clinical response rates at TOC are presented in the Table below.

Table 19: Favourable clinical response rates at TOC

Analysis Population	**Number (%) of patients**	
	CAZ-AVI + MTZ[a] n/N (%)	**Meropenem[b] n/N (%)**
ITT	56/61 (91.8)	21/22 (95.5)
CE	52/56 (92.9)	19/20 (95.5)
Micro-ITT	45/50 (90.0)	18/19 (94.7)
ME	36/40 (90.0)	14/15 (93.3)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

Favourable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure, or clinical improvement, such that no further antimicrobial therapy was required.

CE = clinically evaluable.

ITT = intent-to-treat; the ITT analysis set included all patients who were randomised to treatment.

ME = microbiologically evaluable analysis; the ME analysis set included randomised patients with confirmed cIAI who received a minimum duration of study drug, had a microbiological response other than indeterminate, had no protocol deviations that would impact assessment of efficacy and had a typically IAI bacterial pathogen susceptible to both study agents.

[a] CAZ-AVI doses as per Table 3 with metronidazole 10 mg/kg IV every 8 hours.

[b] 20 mg/kg IV every 8 hours.

The predominant pathogens isolated at baseline were *E. coli* (55/69, 79.7%) and *P. aeruginosa* 23/69 (33.3%). Favourable clinical response rates at TOC by baseline pathogen in the micro-ITT population are presented in the Table below.

Table 20: Favourable clinical response rates at TOC by Baseline Pathogen, Paediatric cIAI (micro-ITT population)

Pathogen	Number (%) of patients	
	CAZ/AVI + MTZ[a] n/N (%)	**Meropenem[b] n/N (%)**
Enterobacterales (Enterobacteriaceae)	38/42 (90.5)	13/14 (92.9)
E. coli	38/42 (90.5)	12/13 (92.3)
Pseudomonas aeruginosa	12/14 (85.7)	8-9 (90.0)

Abbreviations: CAZ/AVI = ceftazidime/avibactam; MTZ = metronidazole.

[a] CAZ/AVI doses as per Table 3 with metronidazole 10 mg/kg IV every 8 hours.

[b] 20 mg/kg IV every 8 hours.

cUTI

A total of 95 paediatric patients with cUTI were randomised (3:1) and received treatment with either CAZ/AVI (n=67) (doses provided in Table 3), or cefepime (n=28), dosed per local prescribing information (maximum dose 2000 mg). After a minimum of 72 hours of IV treatment, there was an optional switch to oral therapy for patients who had clinical improvement, as defined in the study protocol. The total duration of antibiotic therapy (IV plus oral) was between 7 and 14 days. TOC assessments were performed 8 to 15 days after the last dose of study drug (IV or oral).

The majority of patients (83.2%) had acute pyelonephritis (55/67, 82.1% ceftazidime-avibactam; 24/28, 85.7% cefepime). The micro-ITT population included 77 randomised patients (54 ceftazidime-avibactam, 54 cefepime) who had at least 1 Gram-negative typical pathogen known to cause cUTI and no Gram-positive pathogen in the urine at baseline. Favourable clinical, microbiological and combined clinical and microbiological response rates at TOC in the micro-ITT population are presented in the Table below.

Table 21: Favourable clinical and microbiological response rates, paediatric cUTI trial, micro-ITT population

Study Endpoint	CAZ/AVI[a] n/N (%)	Cefepime[b] n/N (%)
Combined favourable clinical and microbiological response	39/54 (72.2)	14/23 (60.9)
Favourable clinical response	48/54 (88.9)	19/23 (82.6)
Favourable microbiological response	43/54 (79.6)	14/23 (60.9)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

[a] Ceftazidime- avibactam doses as per Table 3.

[b] Dosed per local prescribing information, with maximum of 2000 mg.

Favourable clinical response was defined as a resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy was required. Favourable microbiological response was defined as eradication of the baseline pathogen.

The predominant baseline pathogen was *E. coli* (71/77, 92.2%). Favourable microbiological response rates by baseline pathogen at TOC in the micro-ITT population are presented in the Table below.

Table 22: Microbiological response rates by baseline pathogen at TOC in the paediatric cUTI trial, micro-ITT population

Aerobic Gram-Negative Pathogen	CAZ/AVI[a] n/N (%)	Cefepime[b] n/N (%)
Enterobacterales (Enterobacteriaceae)	43/54 (79.6)	14/23 (60.9)
Escherichia coli	39/49 (79.6)	13/22 (59.1)

Abbreviations: CAZ/AVI = ceftazidime/avibactam.

[a] Ceftazidime/avibactam doses as per Table 3.

[b] Dosed per local prescribing information, with maximum of 2000 mg.

Limitations of clinical trial data

Patients with evidence of significant immunocompromise were excluded from the Phase 2 and 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 17 L and 22 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

Adults

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 ≥ 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 precautions 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.

Paediatric population

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 Zavicefta (ceftazidime/avibactam 2000 mg/500 mg) 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 subjects with normal renal function that received Zavicefta (ceftazidime/avibactam 2000 mg/500 mg). 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, and cUTI including dose adjustments for patients with renal impairment, result in systemic exposure and PK/PD target attainment values that are similar to those in adult patients given an approved dose of Zavicefta (CAZ 2000 mg/AVI 500 mg) 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. 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 underexposure in the subjects aged 3 months to < 6 months.

In addition, there are very limited data in paediatric patients aged 3 months to < 2 years with impaired renal function (CrCL ≤ 50 mL/min), 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.

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

Sodium carbonate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2 Dose and method of administration.

6.3 Shelf life

Dry powder

3 years.

After reconstitution

The powder for injection should be reconstituted with water for injections and the resulting solution must then be immediately diluted prior to use. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes. Refer to section 4.2 Dose and method of administration.

After dilution

Infusion bags

For infusion solutions prepared with diluents listed in section 4.2 Dosage and method of administration, the following chemical and physical in-use stability has been demonstrated (from initial vial puncture):

- Infusion solutions with concentration of ceftazidime of 8 mg/mL – up to 12 hours at 2-8°C, followed by up to 4 hours at room temperature.

- Infusion solutions with concentration of ceftazidime of > 8 mg/mL to 40 mg/mL - up to 4 hours at room temperature.

From a microbiological point of view, the medicinal product 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 those above.

Infusion syringes

The chemical and physical in-use stability has been demonstrated (from initial vial puncture) for up to 6 hours at not more than 25°C.

From a microbiological point of view, the medicinal product 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 should not exceed 6 hours at not more than 25°C.

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.

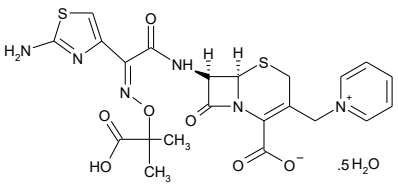
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure

Ceftazidime (as pentahydrate)



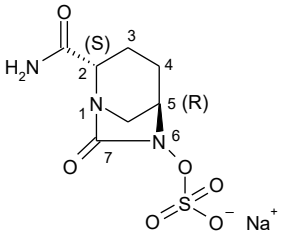
CAS number

78439-06-2.

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.

Chemical structure

Avibactam (as sodium)



CAS number

1192491-61-4.

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

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000.
Toll Free Number: 1800 675 229.
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

22 February 2019

10. DATE OF REVISION

30 September 2026

Summary table of changes

Section changed	Summary of new information
All	Minor editorial changes.
5.1	Inclusion of additional information on the EUCAST breakpoints table, and add disclaimer to specify that prevalence of acquired resistance may vary with geography and time.

Section changed	Summary of new information
8	Update to sponsor website address

® Registered trademark.