

▼ 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 – FETROJA (CEFIDEROCOL) POWDER FOR INJECTION FOR INFUSION

1 NAME OF THE MEDICINE

Cefiderocol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefiderocol sulfate tosilate equivalent to 1 g of cefiderocol.

For the full list of excipients, see [Section 6.1 List of excipients](#).

3 PHARMACEUTICAL FORM

Powder for injection for infusion.

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fetroja is indicated for the treatment of infections due to proven or strongly suspected carbapenem-resistant aerobic Gram-negative organisms in adults with limited treatment options, noting the spectrum of activity of cefiderocol and clinical data ([Section 5.1 Pharmacodynamic properties](#)) and special warnings ([Section 4.4 Special warnings and precautions for use](#)):

Complicated urinary tract infections (cUTIs), including pyelonephritis

Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia

Consideration should be given to official guidance on the appropriate use of antibacterial agents. It is recommended that Fetroja should be used after consultation with a physician with appropriate experience in the management of infectious diseases.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage for adults is 2 g of cefiderocol administered every 8 hours by intravenous (IV) infusion over a 3-hour period. The dosage may be adjusted according to the patient's renal function. The recommended duration of treatment is 7 to 14 days. The duration of therapy should be guided by the patient's clinical status.

Special populations

Renal impairment

Cefiderocol is renally excreted, and high plasma cefiderocol concentrations may be sustained in patients with renal impairment. Dose reduction or other modifications should be considered for patients with renal impairment (CrCl <60 mL/min). In patients with haemodialysis, approximately 60% of cefiderocol in plasma was eliminated by a 3- to 4-hour haemodialysis session.

For patients with renal impairment, the dosage and administration should be adjusted in accordance with the criteria described in [Table 1](#), [Table 2](#) and [Table 3](#).

Table 1 Recommended dose of Fetroja for patients with renal impairment (CrCl <60 mL/min) or patients on haemodialysis *

CrCl (mL/min)/HD patients	Dose per infusion	Dosing interval	Infusion time
30≤CrCl<60	1.5 g	Every 8 hours	3 hours
15≤CrCl<30	1 g	Every 8 hours	3 hours
CrCl<15	0.75 g	Every 12 hours	3 hours
HD patients	0.75 g	Every 12 hours	3 hours

CrCl: Creatinine clearance

*: For patients on haemodialysis (HD patients), Fetroja should be administered as soon as possible after a haemodialysis session.

The dosage and administration for patients receiving continuous renal replacement therapy (CRRT) should be adjusted with reference to the table below.

Table 2 Recommended dose of Fetroja for patients receiving CRRT

Effluent Flow Rate ^a	Dose per infusion	Frequency	Infusion Time
2 L/hr or less	1.5 g	Every 12 hours	3 hours
2.1 to 3 L/hr	2 g	Every 12 hours	3 hours
3.1 to 4 L/hr	1.5 g	Every 8 hours	3 hours
4.1 L/hr or greater	2 g	Every 8 hours	3 hours

CVVH, continuous venovenous haemofiltration; CVVHD, continuous venovenous haemodialysis; CVVHDF, continuous venovenous haemodiafiltration

^a Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF

The dosage and administration for patients with increased renal clearance should be adjusted with reference to the table below.

Table 3 Recommended dose of Fetroja for patients with increased renal clearance

CrCl (mL/min)	Dose per infusion	Dosing interval	Infusion time
CrCl≥120	2 g	Every 6 hours	3 hours

Fetroja does not exhibit activity against Gram-positive and anaerobic bacteria; therefore, if superinfection with these bacterial species is evident, this drug should be administered in combination with antibacterial drugs with activity against these bacterial species.

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Elderly population

No dosage adjustment is required.

Paediatric population

The safety and efficacy of Fetroja in children below 18 years of age has not yet been established. No data are available.

Method of administration

Intravenous use.

Fetroja is administered by intravenous infusion over 3 hours.

Each vial is for single use only.

The powder should be reconstituted with 10 mL of either sodium chloride 9 mg/ml (0.9%) solution for injection, or 5% dextrose injection taken from the 100 mL bags that will be used to prepare the final infusion solution and should be gently shaken to dissolve. The vial(s) should be allowed to stand until the foaming generated on the surface has disappeared (typically within 2 minutes). The final volume of the reconstituted solution in the vial will be approximately 11.2 mL (caution: the reconstituted solution is not for direct injection).

To prepare the required doses, the appropriate volume of reconstituted solution should be withdrawn from the vial according to [Table 4](#). Add the withdrawn volume to the infusion bag containing the remainder of the 100 mL of sodium chloride 9 mg/ml (0.9%) solution for injection, or 5% dextrose injection, inspect the resulting diluted drug product solution in the infusion bag visually for particulate matter and discoloration prior to use. Do not use discoloured solutions or solutions with visible particles.

Table 4 Preparation of Fetroja doses

Fetroja dose	Number of 1 g cefiderocol vials to be reconstituted	Volume to withdraw from reconstituted vial(s)	Total volume of cefiderocol solution required for further dilution in at least 100 mL of 0.9% sodium chloride injection or 5% dextrose injection
2 g	2 vials		22.4 mL

Fetroja dose	Number of 1 g cefiderocol vials to be reconstituted	Volume to withdraw from reconstituted vial(s)	Total volume of cefiderocol solution required for further dilution in at least 100 mL of 0.9% sodium chloride injection or 5% dextrose injection
1.5 g	2 vials	11.2 mL (entire contents) from first vial AND 5.6 mL from second vial	16.8 mL
1 g	1 vial	11.2 mL (entire contents)	11.2 mL
0.75 g	1 vial	8.4 mL	8.4 mL

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

If treatment with a combination of another medicinal product and Fetroja is unavoidable, administration should not occur in the same syringe or in the same infusion solution. It is recommended to adequately flush intravenous lines between administration of different medicinal products.

4.3 CONTRAINDICATIONS

Severe hypersensitivity to the active substance or to any of the excipients listed in [Section 6.1. List of excipients](#).

Severe hypersensitivity (severe systemic allergic reactions such as anaphylaxis occurring) to any other type of betalactam antibacterial agent.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Development of drug resistant bacteria

Prescribing Fetroja in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Hypersensitivity reactions

Hypersensitivity has been reported with cefiderocol.

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibacterial medicinal products may also be hypersensitive to cefiderocol. Before initiating therapy with Fetroja, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics (see [Section 4.3 Contraindications](#)).

If a severe allergic reaction occurs, treatment with Fetroja must be discontinued immediately and adequate emergency measures must be initiated.

Clostridioides difficile-associated diarrhoea

Clostridioides difficile-associated diarrhoea (CDAD) has been reported with cefiderocol. The condition can range in severity from mild diarrhoea to fatal colitis and should be considered in

patients who present with diarrhoea during or subsequent to the administration of Fetroja. Discontinuation of therapy with Fetroja and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

Seizures

Cephalosporins have been implicated in triggering seizures. Patients with known seizure disorders should continue anticonvulsant therapy. Patients who develop focal tremors, myoclonus, or seizures should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If necessary, the dose of Fetroja should be adjusted based on renal function (see [Section 4.2 Dose and method of administration](#)). Alternatively, Fetroja should be discontinued.

Limitations of clinical data

In clinical trials, Fetroja has only been used to treat patients with the following types of infection: complicated urinary tract infections (cUTI); hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), healthcare-associated pneumonia (HCAP); sepsis and patients with bacteraemia (some with no identified primary focus of infection).

The use of Fetroja to treat patients with infections due to Gram-negative aerobic pathogens who have limited treatment options is based on pharmacokinetic-pharmacodynamic analyses for cefiderocol and on limited clinical data from a randomised clinical trial in which 80 patients were treated with Fetroja and 38 patients were treated with best available therapy for infections caused by carbapenem-resistant organisms. No clinical studies have been conducted in patients with central nervous system infections or infections requiring medication for more than 3 weeks (e.g., bone/joint infections, endocarditis).

All-cause mortality in patients with infections due to carbapenem-resistant Gram-negative bacteria

An increase in all-cause mortality was observed in patients treated with cefiderocol as compared to best available therapy (BAT) in a multinational, randomised, open-label trial in critically-ill patients with carbapenem-resistant Gram-negative bacterial infections. Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practises and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections or sepsis. The 28-Day all-cause mortality was higher in patients treated with cefiderocol than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with cefiderocol than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)].

Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Prior to Fetroja administration, consideration should be given to other treatment methods, and if this drug is administered, the patient's condition should be closely monitored (See [Section 5.1 Pharmacodynamic Properties](#)).

Spectrum of activity of cefiderocol

Cefiderocol has little or no activity against the majority of Gram-positive organisms and anaerobes (See [Section 5.1 Pharmacodynamic Properties](#)). Additional antibacterial medicinal products should be used when these pathogens are identified or suspected to be contributing to the infectious process.

Use in renal impairment

The recommended dose adjustments in patients with varying degrees of renal impairment are expected to provide comparable exposures to patients with normal renal function or mild renal impairment (see [Section 4.2 Dose and method of administration](#)). Because the exposure of cefiderocol is dependent on renal function, monitor CrCL and adjust the dose of cefiderocol accordingly for patients with changing renal function.

Use in the elderly

cUTI

Of the 300 patients treated with FETROJA in the cUTI trial, 158 (52.7%) were 65 years of age and older, and 67 (22.3%) were 75 years of age and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Hospital-acquired pneumonia (HABP)/Ventilator-associated bacterial pneumonia (VABP)

Of the 148 patients treated with FETROJA in the HABP/VABP trial, 83 (56.1%) were 65 years of age and older, and 40 (27.0%) were 75 years of age and older.

The incidence of adverse events in patients treated with FETROJA was similar in patients younger than 65 years of age as compared to older patients (65 years of age and older and 75 years of age and older). The incidence of adverse reactions in older patients (65 years of age and older and 75 years of age and older) was also similar between the treatment groups.

Clinical cure rates at the Test-of-Cure visit (TOC) in FETROJA-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age, and 75 years of age and older were 60.0%, 77.5%, and 60.0%, respectively. In comparison, the clinical cure rates at TOC in the meropenem-treated patients for each of these subgroups were 65.5%, 64.4%, and 70.5%, respectively. The observed all-cause mortality rates at Day 14 in the FETROJA-treated patients for each of these subgroups were 12.3%, 7.5%, and 17.5%, respectively.

In comparison, in the meropenem-treated patients for each of these subgroups, they were 10.3%, 17.8%, and 9.1%, respectively.

CREDIBLE-CR

Of the 101 patients treated with FETROJA in the CREDIBLE-CR trial, 64 (63.4%) were 65 years of age and older.

There were no important differences in the incidence of adverse events between these patients and younger patients.

Clinical cure rates at TOC in FETROJA-treated adult patients younger than 65 years of age and 65 years of age and older were 50.0% and 54.0%, respectively. In comparison, the clinical cure rates at TOC in the BAT patients for each of these subgroups were 61.9% and 35.3%, respectively.

The microbiological eradication rates at TOC in FETROJA-treated adult patients younger than 65 years of age and 65 years of age and older were 30.0% and 32.0%, respectively. In comparison, the microbiological eradication rates at TOC visit in the BAT patients for each of these subgroups were 38.1% and 5.9%, respectively.

cUTI and HABP/VABP

FETROJA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

No dosage adjustment is required based on age. Dosage adjustment for elderly patients should be based on renal function (see [Section 4.2 Dose and method of administration](#) and [5.2 Pharmacokinetic properties](#)).

Paediatric use

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

Effects on laboratory tests

Cefiderocol may show false-positive results in dipstick tests for urine protein, urine ketone bodies, and urine occult blood.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies suggest potential for cefiderocol sulfate tosilate to inhibit CYP450 enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at clinically relevant concentrations (IC₅₀ values >1330 µM [>5320 µM for CYP2C8]). However, in two phase 1 clinical studies, no significant drug-drug interactions were noted between cefiderocol and substrates of cytochrome P450 enzymes.

Similarly, *in vitro*, cefiderocol also exhibited inhibitory activity against the renal transporters OAT1 and OAT3 (IC₅₀ value ranging 141 - 292 µM) indicating potential for clinically relevant interactions. However, no significant drug-drug interactions were noted between cefiderocol and substrates of transporters in two phase I clinical studies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of cefiderocol on fertility in humans has not been studied. Based on a rat fertility study, cefiderocol, administered intravenously at doses up to 1000 mg/kg/day (exposure similar to the clinical AUC, approximately ER_{AUC} of 1.1), had no effect on male or female fertility.

Use in pregnancy – Pregnancy Category B1

Fetroja should be administered to women who are or may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with this treatment. In embryofetal development studies conducted with rats and mice, cefiderocol, administered intravenously or subcutaneously at doses up to 1000 mg/kg/day (exposure similar to the clinical AUC) and 2000 mg/kg/day (1.6-fold exposure relative to clinical AUC), respectively, no effect on embryofetal development was observed.

In a pre-/post-natal development study in rats, cefiderocol, administered intravenously at doses up to 1000 mg/kg/day (exposure similar to the clinical AUC), yielded no pre/postnatal developmental concerns. Based on a distribution study in rats, placental transfer of cefiderocol was confirmed.

Use in lactation.

For breast-feeding women, continuation or discontinuation of breast-feeding should be considered in view of the therapeutic benefits of Fetroja and the benefits of breast-feeding. Cefiderocol has been reported to be excreted in milk in animal studies (in rats).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Fetroja has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile in clinical studies

The safety of Fetroja was evaluated in a total of 549 subjects who participated in one Phase 2 and two Phase 3 clinical efficacy and safety studies.

In the phase 2 study (APEKS-cUTI), 300 subjects received Fetroja 2 g every 8 hours infused over 1 hour (or a renally-adjusted dose), and 148 subjects were treated with imipenem/cilastatin 1g/1g every 8 hours infused over 1 hour (or a renally-adjusted dose). The incidence rate of adverse events was 40.7% (122/300) subjects in the cefiderocol group, with the most common adverse events including diarrhoea 4.3%, and hypertension 4.3%.

A total of 148 subjects entered the second phase 3 study (APEKS-NP). They received Fetroja 2 g every 8 hours, for 7 to 15 days. The incidence rate of adverse events was 87.8 %, with the most common adverse events including urinary tract infection 15.5%, and hypokalaemia 10.8 %.

In the first phase 3 comparative study (CREDIBLE-CR), a total of 101 received Fetroja 2 g every 8 hours, for 7 to 14 days and up to 21 days in some cases. The incidence rate of adverse events was 91.1% (92/101) subjects in the cefiderocol group, with the most common adverse events including diarrhoea 18.8%, pyrexia 13.9 %, septic shock 12.9% and vomiting 12.9%.

Adverse events reported in $\geq 2\%$ of subjects in the phase 2 study and $\geq 5\%$ of subjects in the phase 3 studies are summarised in Table 5, Table 6 and Table 7 below.

Table 5 Adverse events occurring in $\geq 2\%$ of subjects in either treatment group (APEKS-cUTI)

Preferred Term	Fetroja (cefiderocol) (N = 300) n (%)	Imipenem/Cilastatin (N = 148) n (%)
Subjects with AEs	122 (40.7)	76 (51.4)
Diarrhoea	13 (4.3)	9 (6.1)
Hypertension	13 (4.3)	8 (5.4)
Constipation	10 (3.3)	6 (4.1)
Infusion site pain	9 (3.0)	5 (3.4)
Headache	7 (2.3)	8 (5.4)
Nausea	7 (2.3)	6 (4.1)
Cough	7 (2.3)	1 (0.7)
Vomiting	6 (2.0)	2 (1.4)
Hypokalaemia	5 (1.7)	4 (2.7)
Renal cyst	4 (1.3)	5 (3.4)
Insomnia	4 (1.3)	3 (2.0)
Infusion site erythema	3 (1.0)	3 (2.0)
Abdominal pain upper	2 (0.7)	5 (3.4)
Cardiac failure	2 (0.7)	3 (2.0)
Clostridium difficile colitis	1 (0.3)	4 (2.7)
Vaginal infection	1 (0.3)	3 (2.0)

Table 6 Adverse events occurring in $\geq 5\%$ of subjects in either treatment group (APEKS-NP)

Preferred Term	Fetroja (cefiderocol) (N = 148) n (%)	Meropenem (N = 150) n (%)
Subjects with AEs	130 (87.8)	129 (86.0)
Urinary tract infection	23 (15.5)	16 (10.7)
Hypokalaemia	16 (10.8)	23 (15.3)
Diarrhoea	13 (8.8)	13 (8.7)
Anaemia	12 (8.1)	12 (8.0)
Pleural effusion	10 (6.8)	6 (4.0)

Preferred Term	Fetroja (cefiderocol) (N = 148)	Meropenem (N = 150)
	n (%)	n (%)
Aspartate aminotransferase increased	10 (6.8)	6 (4.0)
Alanine aminotransferase increased	9 (6.1)	6 (4.0)
Hypomagnesaemia	8 (5.4)	1 (0.7)
Hypoalbuminaemia	5 (3.4)	8 (5.3)
Hepatic enzyme increased	4 (2.7)	10 (6.7)
Hyponatraemia	4 (2.7)	10 (6.7)
Decubitus ulcer	4 (2.7)	10 (6.7)
Hypotension	2 (1.4)	10 (6.7)
Thrombocytopenia	2 (1.4)	8 (5.3)

Table 7 Adverse events occurring in ≥ 5% of subjects in either treatment group (CREDIBLE-CR)

Preferred Term	Fetroja (cefiderocol) (N = 101)		BAT (N = 49)	
	n (%)		n (%)	
Subjects with adverse events	92	(91.1)	47	(95.9)
Diarrhoea	19	(18.8)	6	(12.2)
Pyrexia	14	(13.9)	6	(12.2)
Septic shock	13	(12.9)	7	(14.3)
Vomiting	13	(12.9)	7	(14.3)
Decubitus ulcer	10	(9.9)	4	(8.2)
Hypokalaemia	9	(8.9)	7	(14.3)
Liver function test abnormal	8	(7.9)	4	(8.2)
Constipation	8	(7.9)	3	(6.1)
Hypotension	8	(7.9)	3	(6.1)
Anaemia	8	(7.9)	2	(4.1)
Aspartate aminotransferase increased	8	(7.9)	1	(2.0)
Pleural effusion	8	(7.9)	1	(2.0)
Acute kidney injury	7	(6.9)	5	(10.2)
Dyspnoea	7	(6.9)	2	(4.1)
Nausea	7	(6.9)	2	(4.1)
Pneumonia	7	(6.9)	1	(2.0)
Alanine aminotransferase increased	7	(6.9)	0	
Abdominal pain	6	(5.9)	4	(8.2)
Hypomagnesaemia	6	(5.9)	4	(8.2)
Thrombocytopenia	6	(5.9)	4	(8.2)
Chest pain	6	(5.9)	0	
Hyperkalaemia	5	(5.0)	6	(12.2)
Agitation	5	(5.0)	2	(4.1)
Oedema peripheral	5	(5.0)	2	(4.1)
Sepsis	4	(4.0)	3	(6.1)
Rash	3	(3.0)	4	(8.2)
Bradycardia	3	(3.0)	3	(6.1)
Metabolic acidosis	3	(3.0)	3	(6.1)
Insomnia	2	(2.0)	3	(6.1)
Depression	0		3	(6.1)

BAT= Best Available Therapy

Tabulated list of adverse reactions

Adverse reactions are classified according to frequency and System Organ Class (SOC). Frequency categories are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each System Organ Class, undesirable effects are presented in order of decreasing seriousness. Table 8 shows the tabulated list of common adverse reactions reported with Fetroja in the Phase 2 and 3 studies (i.e. APEKS-cUTI, CREDIBLE-CR and APEKS-NP study).

Table 8 Tabulated list of adverse reactions occurring in 1% or greater in the Phase 2 and 3 studies

System organ class	Common ($\geq 1/100$ to $< 1/10$)
Skin and subcutaneous tissue disorders	Rash, rash macular, rash maculo-papular, rash erythematous and drug eruption
Respiratory, thoracic and mediastinal disorders	Cough
Investigations	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Gamma- glutamyltransferase (GGT) increased, Hepatic function abnormal, liver function test increased, hepatic enzyme increased, transaminases increased and liver function test abnormal
Gastrointestinal disorders	Diarrhoea, Nausea, vomiting
Infections and infestations	Candida infection, oral candidiasis, vulvovaginal candidiasis, candiduria, <i>Clostridium difficile</i> colitis, pseudomembranous colitis and <i>Clostridium difficile</i> infection
General disorders and administration site conditions	Infusion site reaction, infusion site pain, injection site pain, infusion site erythema and injection site phlebitis

Less common adverse reactions in the Phase 2 and 3 studies

The following adverse reactions were reported with Fetroja at a rate of less than 1% in the Phase 2 and 3 studies:

Skin and subcutaneous tissue disorders: Pruritus

Post marketing experience

The following adverse reactions have been identified during post approval use of the medicinal product. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Neutropenia, Eosinophilia

Renal and urinary disorders: Chromaturia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on clinical signs and symptoms associated with an overdose of cefiderocol.

In the event of overdose, patients should be monitored, and treatment discontinuation and general supportive treatment should be considered.

Approximately 60% of cefiderocol is removed by a 3- to 4-hour haemodialysis session.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01DI04.

Mechanism of action

Cefiderocol is a siderophore cephalosporin. In addition to passive diffusion through outer membrane porin channels, cefiderocol is able to bind to extracellular free iron via its siderophore side chain, allowing active transport into the periplasmic space of Gram-negative bacteria through siderophore uptake systems. Cefiderocol subsequently binds to penicillin binding proteins (PBPs), inhibiting bacterial peptidoglycan cell wall synthesis which leads to cell lysis.

Resistance

Mechanisms of bacterial resistance that may lead to resistance to cefiderocol include mutation of PBPs; beta-lactamase enzymes with ability to hydrolyse cefiderocol; mutations affecting regulation of bacterial iron uptake; mutations in siderophore transport proteins; overexpression of native bacterial siderophores.

The *in vitro* antibacterial activity of cefiderocol is not affected by the majority of beta-lactamases, including metallo-enzymes. Due to the siderophore-mediated mode of cell entry, the *in vitro* activity of cefiderocol activity is generally less affected by porin loss or efflux-mediated resistance compared to many other beta-lactam agents.

Cefiderocol has little or no activity against Gram-positive or anaerobic bacteria due to intrinsic resistance.

Interaction with Other Antimicrobials:

In vitro studies showed no antagonism between cefiderocol and amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline, or vancomycin.

In vitro studies have demonstrated additive or synergist effects against strains of Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, including multi-drug resistant strains, when cefiderocol was combined with amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem, ciprofloxacin or colistin.

List of microorganisms

At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the 4 µg/mL for cefiderocol:

Gram negative

Acinetobacter baumannii complex

Achromobacter species

Burkholderia cepacia complex

Burkholderia pseudomallei

Citrobacter freundii complex

Citrobacter koseri

Enterobacter cloacae complex

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Klebsiella aerogenes

Morganella morganii

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Pseudomonas aeruginosa

Serratia marcescens

Stenotrophomonas maltophilia

Acinetobacter baumannii complex comprises 4 species: *A. calcoaceticus* (genomic species 1, an environmental species of limited clinical significance), *A. baumannii* (genomic species 2), *A. pittii* (genomic species 3) and *A. nosocomialis* (genomic species 13TU).

Burkholderia cepacia complex comprises 9 species: *B. cepacia* (formerly genomovar I), *B. multivorans* (genomovar II), *B. cenocepacia* (genomovar III), *B. stabilis* (genomovar IV), *B. vietnamiensis* (genomovar V), *B. dolosa* (genomovar VI), *B. ambifaria* (genomovar VII), *B. anthina* (genomovar VIII), and *B. pyrrocinia* (genomovar IX).

Citrobacter freundii complex comprises 11 species: *C. braakii*, *C. freundii*, *C. gillenii*, *C. murlinae*, *C. sedlakii*, *C. werkmani*, *C. youngae* and 3 non-named species. *Enterobacter cloacae* complex comprises 6 species: *E. cloacae*, *E. asburiae*, *E. hormaechei*, *E. kobei*, *E. ludwigii* and *E. nimipressuralis*.

Pharmacodynamic effects

With beta-lactam antimicrobial drugs, the time that unbound plasma concentrations exceed the minimum inhibitory concentration (%fT_{>MIC}) against the infecting organism has been shown to best correlate with efficacy, as has been demonstrated with cefiderocol in neutropenic murine thigh and lung infection models with Enterobacterales, *P. aeruginosa* and *A. baumannii*. The time above a threshold concentration has been determined to be the parameter that best predicts the efficacy of cefiderocol in *in vivo* nonclinical models. In an immunocompetent rat pneumonia model and neutropenic murine thigh model reproducing human drug exposure, 2 g of cefiderocol q8h with a 3-hour infusion showed the microbiological eradication of Enterobacterales, *P. aeruginosa* and *A. baumannii* including carbapenem-resistant strains.

Cardiac Electrophysiology

At dosages of 2 g and 4 g, cefiderocol does not prolong the QT interval to any clinically relevant extent.

Clinical trials

APEKS-cUTI study (1409R2121)

This was a phase 2, multicentre, double-blind, randomised, active-controlled study to assess the efficacy and safety of Fetroja in complicated urinary tract infections (cUTI) with or without pyelonephritis or acute uncomplicated pyelonephritis caused by Gram-negative pathogens in hospitalised adults in comparison with intravenous imipenem/cilastatin (IPM/CS). The subjects were randomised (2:1) to either Fetroja (intravenous cefiderocol) 2 g or IPM/CS (1/1 g) over 1 hour, every 8 hours for 7 to 14 days. Four hundred forty-eight subjects were treated, and 371 subjects met the definition of the Microbiological Intent-to-treat (Micro-ITT) Population, defined as subjects having taken at least 1 dose of the study drug and with a Gram-negative uropathogen at baseline. For clinical diagnosis at baseline in Micro-ITT population in the Fetroja group and the IPM/CS group (hereinafter the same order), 25.8% (65/252) and 24.4% (29/119) of subjects had cUTI with pyelonephritis, 48.4% (122/252) and 46.2% (55/119) of subjects had cUTI without pyelonephritis, and 25.8% (65/252) and 29.4% (35/119) of subjects had acute uncomplicated pyelonephritis.

The most frequently reported Gram-negative uropathogens isolated at baseline for both cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis in the Micro-ITT Population were *E. coli* (60.3% [152/252] of subjects in the Fetroja group and 66.4% [79/119] of subjects in the IPM/CS group) and *K. pneumoniae* (19.0% [48/252] of subjects in the Fetroja group and 21.0% [25/119] of subjects in the IPM/CS group).

For the primary composite endpoint of both clinical cure (improvement or resolution of clinical signs and symptoms of cUTI assessed by the investigator) and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $< 10^4$ colony forming units/mL) at TOC (7 ± 2 days after the last dose of study drug) for the Micro-ITT Population, the response rate was 72.6% (183/252 subjects) for Fetroja and 54.6% (65/119 subjects) for IPM/CS.

The adjusted treatment difference of 18.58% (95% confidence interval [CI]; 8.23%, 28.92%) in favour of Fetroja met the criteria to demonstrate noninferiority with a prespecified 20% and 15% margin as shown in Table 9.

Table 9 Composite, microbiological and clinical response rates at TOC

Study Endpoint	Fetroja(cefiderocol) n/N (%)	Imipenem/cilastatin n/N (%)	Treatment Difference (95% CI) ^a
Composite response at TOC Micro-ITT	183/252 (72.6%)	65/119 (54.6%)	18.58 (8.23, 28.92)
Micro response TOC Micro-ITT	184/252 (73.0%)	67/119 (56.3%)	17.25 (6.92, 27.58)
Clinical response TOC Micro-ITT	226/252 (89.7%)	104/119 (87.4%)	2.39 (-4.66, 9.44)

a The 95% confidence interval was based on Cochran-Mantel-Haenzel method.

The most frequently observed adverse event was diarrhoea, which was experienced by 4.3% (13/300 subjects) and 6.1% (9/148 subjects) of Fetroja- and IPM/CS-treated subjects, respectively.

APEKS-NP study (1615R2132)

This was a Phase 3, multicentre, double-blind, parallel-group, randomised, active-controlled study to assess the efficacy and safety of Fetroja (intravenous cefiderocol) in comparison with high-dose, extended-infusion meropenem in hospitalised adults with HABP, VABP, or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens. The subjects were randomised (1:1) to either Fetroja (2 g) or meropenem (2 g) over 3 hours, every 8 hours for 7 to 14 days. Of 298 treated subjects, 292 subjects met the definition of the Modified Intent-to-treat (mITT) Population (145 in the Fetroja group and 147 in the meropenem group), defined as all randomised subjects who received at least 1 dose of study drug, who either had evidence of:

- a Gram-negative infection of the lower respiratory tract based on microbiological culture, OR
- a lower respiratory tract infection, but culture did not provide a microbiological diagnosis.

Note: Subjects with bacterial pneumonia caused by Gram-positive aerobic or anaerobic (Gram positive or Gram-negative) bacteria only were excluded from the mITT population.

The most frequently reported Gram-negative pathogens isolated at baseline for both groups in the mITT Population were *K. pneumoniae* (33.1% [48/145] of subjects in the Fetroja group and 29.9% [44/147] of subjects in the meropenem group), *P. aeruginosa* (16.6% [24/145] and

16.3% [24/147]), *A. baumannii* (15.9% [23/145] and 16.3% [24/147]), and *E. coli* (13.1% [19/145] and 15.0% [22/147]).

The all-cause mortality rates by time point after the start of study drug therapy are shown in Table 10. The all-cause mortality at Day 14 (the primary efficacy endpoint) was 12.4% (18/145) in the Fetroja group and 11.6% (17/146) in the meropenem group. Noninferiority of Fetroja to meropenem was demonstrated since the upper limit of the 95% confidence interval for the treatment difference in the Day 14 all-cause mortality was less than 12.5% (95% CI: -6.6, 8.2).

Table 10 All-cause mortality, clinical cure rates, and microbiological eradication at TOC (modified intent-to-treat population)

Study Endpoint	Fetroja (cefiderocol) n/N (%) (N=145)	Meropenem n/N (%) (N=147)	Treatment Difference (95% CI) ^a
Day 14 All-cause Mortality ^b	N'=145 18/145 (12.4)	N'=146 17/146 (11.6)	0.8 (-6.6, 8.2)
Clinical Cure at TOC	94/145 (64.8)	98/147 (66.7)	-2.0 (-12.5, 8.5)
Microbiological Eradication at TOC ^c	N*=124 59/124 (47.6)	N*=127 61/127 (48.0)	-1.4 (-13.5, 10.7)

a The adjusted treatment difference (Fetroja minus meropenem) and associated 95% CI were based on the Cochran-Mantel-Haenszel method.

b Percentage is calculated using N' as the denominator where N' is the number of subjects with known survival status.

c Percentage is calculated using N* as the denominator where N* is the number of subjects with nonmissing baseline pathogens.

The most frequently observed AEs were urinary tract infection (15.5% [23/148 subjects] and 10.7% [16/150 subjects] in the Fetroja and meropenem groups, respectively) and hypokalaemia (10.8% [16/148 subjects] and 15.3% [23/150 subjects] in the Fetroja and meropenem groups, respectively).

CREDIBLE-CR study (1424R2131)

This was a Phase 3, multicentre, open-label, randomised, active-controlled study to assess the efficacy and safety of Fetroja (intravenous cefiderocol) in adults with the following infections caused by a carbapenem-resistant Gram-negative pathogen: hospital-acquired pneumonia (HAP)/ventilator-acquired pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or cUTI or bloodstream infections (BSI)/sepsis. The subjects assessed by the investigator to require 7-14 days of intravenous treatment in hospital are randomised (2:1) to either Fetroja (2 g) over 3 hours, every 8 hours or best available therapy (BAT) depending on the identified pathogen and the site of infection.

Of 150 treated subjects, 118 subjects met the definition of the Carbapenem-Resistant Microbiological Intent-to-treat (Micro-ITT) Population (80 in the Fetroja group and 38 in the BAT group), defined as subjects having taken at least 1 dose of the study drug and with a carbapenem-resistant Gram-negative pathogen at baseline.

In the CR Micro-ITT population, for all infection sites combined, the most frequently reported Gram-negative pathogens isolated at baseline for both groups were *A. baumannii* (46.3% [37/80] of subjects in the Fetroja group and 44.7% [17/38] of subjects in the BAT group), *K. pneumoniae* (40.0% [32/80] and 31.6% [12/38]), and *P. aeruginosa* (21.3% [17/80] and 28.9% [11/38]). The primary efficacy outcomes at TOC for Carbapenem-Resistant Micro-ITT Population is summarised in Table 11.

For all infection sites combined, the clinical cure rate was 52.5% (42/80 subjects) for Fetroja and 50.0% (19/38 subjects) for BAT. The microbiological eradication rate was 31.3% (25/80 subjects) for Fetroja and 23.7% (9/38 subjects) for BAT.

For all infection sites combined, all-cause mortality was 24.8% (25/101 subjects) and 18.4% (9/49 subjects) [treatment difference 6.4%, 95% CI (-8.6, 19.2)] at Day 28, and 33.7% (34/101 subjects) and 18.4% (9/49 subjects) [treatment difference 15.3%, 95% CI (-0.2, 28.6)] at end-of-study (EOS) in the Fetroja and BAT groups, respectively.

Table 11 Primary efficacy outcome at TOC (carbapenem-resistant microbiological intent-to-treat population)

Study Endpoint	Fetroja (cefiderocol) n/N (%) (N=80)	(95% CI) ^a	BAT n/N (%) (N=38)	(95% CI) ^a
HAP/VAP/HCAP				
Clinical Cure at TOC	20/40 (50.0)	(33.8, 66.2)	10/19 (52.6)	(28.9, 75.6)
BSI/Sepsis				
Clinical Cure at TOC	10/23 (43.5)	(23.2, 65.5)	6/14 (42.9)	(17.7, 71.1)
cUTI				
Microbiological Eradication at TOC	9/17 (52.9)	(27.8, 77.0)	1/5 (20.0)	(0.5, 71.6)
All Infection Sites Combined				
Clinical Cure at TOC	42/80 (52.5)	(41.0, 63.8)	19/38 (50.0)	(33.4, 66.6)
Microbiological Eradication at TOC	25/80 (31.3)	(21.3, 42.6)	9/38 (23.7)	(11.4, 40.2)

a The 95% confidence interval was based on Clopper-Pearson method.

The most frequently observed adverse event was diarrhoea, which was experienced by 18.8% (19/101 subjects) and 12.2% (6/49 subjects) of Fetroja- and BAT-treated subjects, respectively.

5.2 PHARMACOKINETIC PROPERTIES

Figure 1 shows the plasma concentrations of cefiderocol in 6 healthy adult subjects following single 1-hour intravenous (IV) infusions of Fetroja 100 mg, 250 mg, 500 mg, 1 g, and 2 g, and Table 12 shows the pharmacokinetic parameters of cefiderocol following a single IV infusion or repeated every 8-hour IV infusions of Fetroja 2 g. Cefiderocol C_{max} and AUC increased dose-proportionally. The pharmacokinetics of cefiderocol following repeated administration were almost the same as those following single administration, showing no drug accumulation.

Figure 1 Mean plasma concentration-time curves following single administration of cefiderocol (healthy adults)

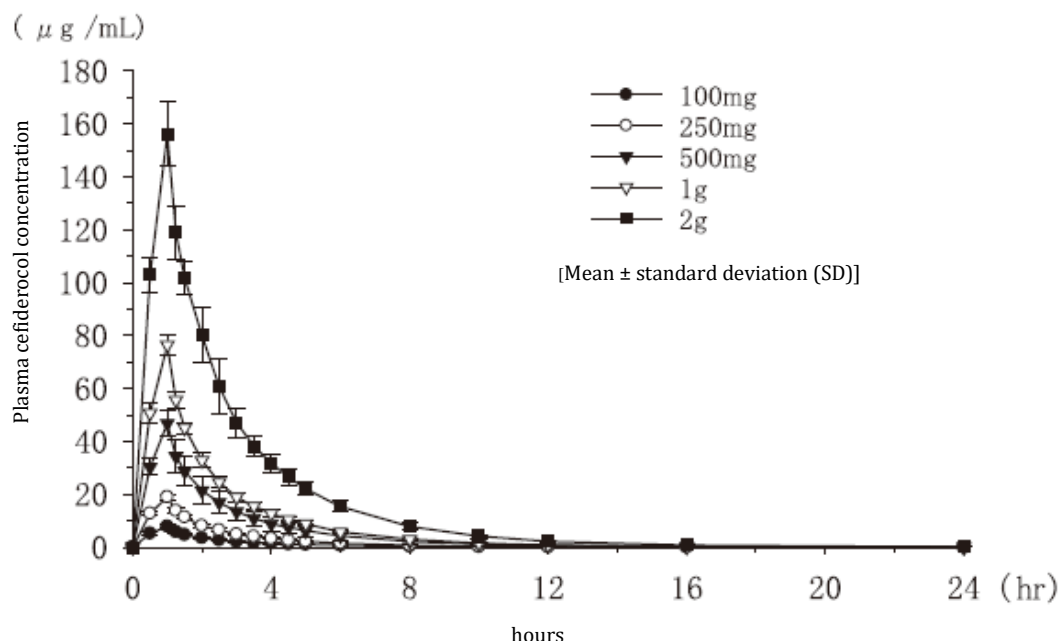


Table 12 Cefiderocol pharmacokinetic parameters

Dose (g)	Infusion time (hrs)	Number of subjects	C _{max} (µg/mL)	AUC (µg•hr/mL)	T _{1/2} (hr)
Single administration					
2	1	6	156(7.9)	389.7(9.0)	2.74(10.2)
2	3	43	89.7(20.5)	386.1(17.2)	2.41(14.0)
Repeated administration (for 10 days)					
2	1	8	153(12.9)	366.5(14.0)	2.72(21.6)

(Measurement method: LC/MS/MS) (geometric mean [% geometric coefficient of variation (CV)])

Distribution

The binding of cefiderocol to human plasma proteins, primarily albumin, is in the range of 40 to 60%, the geometric mean (CV%) volume of distribution during the terminal phase of cefiderocol in healthy adult subjects (n = 43) after intravenous administration of a single 2 g dose of cefiderocol was 18.0 L (18.1%), similar to extracellular fluid volume.

Following a cefiderocol 2 g dose (or renal function equivalent dose) at steady state in patients with pneumonia requiring mechanical ventilation with a 3-hour infusion, the cefiderocol concentrations in epithelial lining fluid ranged 3.1 to 20.7 µg/mL and 7.2 to 15.9 µg/mL at the end of infusion and at 2 hours after the end of infusion, respectively.

Metabolism

After administration of a single 1 g dose of [¹⁴C]-labelled cefiderocol infused over 1 hour, cefiderocol accounted for 92.3% of the plasma AUC for total radioactivity.

Excretion

After administration of a single 1 g dose of [¹⁴C]-labelled cefiderocol infused over 1 hour, the amount of total radioactivity excreted in urine was 98.6% of the administered dose, with 2.8% of the administered dose excreted in faeces. The amount of unchanged cefiderocol excreted in urine was 90.6% of the administered dose.

Patients with renal impairment

The pharmacokinetics of cefiderocol after administration of a single 1 g dose was assessed in patients with normal renal function, patients with mild, moderate or severe renal impairment, and patients with end stage renal failure requiring haemodialysis. The AUC of cefiderocol increased with the increase in the severity of renal impairment as shown in Table 13. The membrane permeation clearance of cefiderocol during continuous renal replacement therapy was dependent on the inflow rate of the filtrate or dialysate in an *in vitro* dialysis experiment. Exposure to cefiderocol may be reduced in patients receiving continuous renal replacement therapy.

Table 13 Cefiderocol AUC according to the degree of renal function

Degree of renal function (estimated glomerular filtration rate: eGFR) (mL/min/1.73 m ²)	Number of subjects	AUC _{0-inf} (μg•hr/mL)	
		Geometric mean	Ratio to subjects with normal renal function [90% confidence interval (CI)]
Subjects with normal renal function	8	213.4	
Subjects with mild renal impairment (≥60 to <90)	8	218.7	1.025 [0.817, 1.287]
Subjects with moderate renal impairment (≥30 to <60)	7	312.3	1.464 [1.157, 1.852]
Subjects with severe renal impairment (≥15 to <30)	6	543.2	2.546 [1.992, 3.254]
Subjects with end stage renal failure (Administration following haemodialysis)	8	880.7	4.128 [3.289, 5.181]

Patients with increased renal clearance

Table 14 shows the estimated total body clearance (CL) of cefiderocol in patients with increased renal clearance (CrCL ≥120 mL/min) and patients with normal renal function (CrCL ≥90 to <120 mL/min) based on the results of the population pharmacokinetic analyses of data from a global phase III study in patients with nosocomial pneumonia. Increased CL was observed in patients with increased renal clearance.

Table 14 Total body clearance of cefiderocol in patients with increased renal clearance and patients with normal renal function

CrCL (mL/min)	Number of subjects	CL (L/hr) *1
120≤CrCL	19	6.46(38.0)
90≤CrCL<120	27	4.48(66.0)

※1: Geometric mean by Bayesian estimation (% geometric CV)

Drug interaction studies

Clinical trials

Co-administration with 2 g doses of Fetroja given every 8 hours did not affect the pharmacokinetics of midazolam (a CYP3A substrate), furosemide (an OAT1 and OAT3 substrate) or metformin (an OCT1, OCT2, and MATE2-K substrate). Co-administration with 2 g doses of Fetroja given every 8 hours increased rosuvastatin (a OATP1B3 substrate) AUC by 21%, which was considered not to be clinically meaningful.

In vitro studies

In the *in vitro* study at clinically relevant concentrations, cefiderocol did not inhibit the major CYP enzymes; no concentration- or time-dependent inhibitions of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 enzymes were observed and cefiderocol did not induce CYP1A2, 2B6, or 3A4 enzymes.

Cefiderocol is not a substrate of drug transporters including OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP. Cefiderocol is also considered not to be an inhibitor of gut, renal or hepatic transporters including OATP1B1, MATE1, P-gp, BCRP, or BSEP transporters.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cefiderocol was negative for mutagenicity in an *in vitro* reverse mutation test with bacteria and in the *in vitro* HPRT gene mutation assay in human cells. Positive findings were seen in an *in vitro* chromosomal aberration test in cultured TK6 cells and an *in vitro* mouse lymphoma assay (MLA).

However, no genotoxicity was noted in an *in vivo* rat micronucleus study and a rat comet assay at doses up to 2000 mg/kg and 1500 mg/kg, respectively. Based on C_0 values for rats administered 1500 mg/kg/day in the repeat dose toxicity studies, sufficient C_{max} -based animal:human safety margins ($ER_{C_{max}} > 29$) were achieved in the *in vivo* genotoxicity studies to support the claim of no clastogenic or DNA-damaging potential for cefiderocol.

Carcinogenicity

No carcinogenicity studies were conducted with cefiderocol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose
Sodium chloride
Sodium hydroxide (pH adjustment)

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](#).

If treatment with a combination of another medicinal product and Fetroja is unavoidable, administration should not occur in the same syringe or in the same infusion solution. It is recommended to adequately flush intravenous lines between administration of different medicinal products.

6.3 SHELF LIFE

Powder

5 years

Stability of reconstituted solution in the vial

Chemical and physical in-use stability after reconstitution has been demonstrated for 1 hour at 25°C.

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not be more than 1 hour at 25°C.

Stability of the diluted solution in the infusion bag

Chemical, microbiological and physical in-use stability after dilution has been demonstrated for 6 hours at 25°C and for 24 hours at 2 to 8°C protected from light, followed by 6 hours at 25°C.

From a microbiological point of view, diluted products should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 6 hours at 25°C or 24 hours at 2 to 8°C protected from light, followed by 6 hours at 25°C, unless dilution has taken place in controlled and validated aseptic conditions. The 6-hour period at 25°C should be inclusive of the product administration period of 3 hours. If storing the infusion solution in the refrigerator, the infusion bag should be removed and allowed to reach room temperature prior to use.

For preparation of solution for administration, see [Section 4.2 Dose and method of administration](#).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C.

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

For storage conditions after reconstitution and dilution of the medicinal product, see [Section 6.3 Shelf life](#).

6.5 NATURE AND CONTENTS OF CONTAINER

14 mL vial (Type I clear glass vial), chlorobutyl elastomeric stopper, and aluminium seal with a plastic flip-off cap. The vials are packed in a cardboard carton.

Pack size of 10 vials.

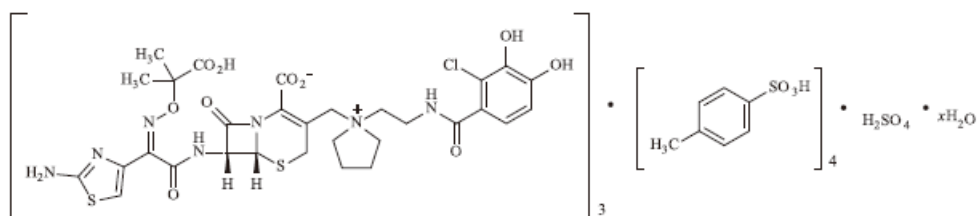
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

This medicinal product is for single use in one patient only.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1225208-94-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Accelagen Pty Ltd
Suite 2.02/785 Toorak Road,
Hawthorn East, VIC, 3123
Australia
Phone: +61 (03) 9114 2270
info@accelagen.com.au

9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information