



Australian Government

Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Fetroja

Active ingredient: Cefiderocol (as sulfate
tosilate)

Sponsor: Accelagen Pty Ltd

October 2026

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
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Contents

List of abbreviations	4
Product submission	6
Submission details	6
Product background	7
Disease or condition	7
Current treatment options	8
Clinical rationale	9
Regulatory status	10
Australian regulatory status	10
International regulatory status	10
Registration timeline	12
Assessment overview	12
Quality evaluation summary	12
Drug substance	12
Drug product	13
Nonclinical evaluation summary	14
Clinical evaluation summary	15
Pharmacology	15
Efficacy	17
Safety	24
Risk management plan	25
Recommendation following the clinical evaluation	26
Risk-benefit analysis	26
Advisory Committee considerations	27
Advisory committee conclusion	28
Section 60 review and outcome	29
Assessment outcome	30
Specific conditions of registration	31
Product Information and Consumer Medicine Information	31

List of abbreviations

Abbreviation	Meaning
%fT > MIC	The percentage of the dosing interval required for free-drug plasma concentration to exceed the minimum inhibitory concentration
ACM	Advisory Committee on Medicines
AEs	Adverse events
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
AUC _{0-inf}	Area under the plasma concentration-time curve extrapolated from time zero to infinity
BSI	Bloodstream infection
CI	Confidence intervals
CMI	Consumer Medicines Information
cUTIs	Complicated urinary tract infection(s)
C _{max}	Maximum concentration
FU	Follow-up
EA	Early Assessment
EOT	End of Treatment
GM	Geometric mean
HCABP	Healthcare-associated bacterial pneumonia
HCAP	Healthcare-associated pneumonia
HAP	Hospital-acquired pneumonia
IPM/CS	imipenem/cilastatin
MIC	minimum inhibitory concentration
Micro-ITT	microbiological intent-to-treat population
mITT	Modified Intent-to-Treat population
PI	Product Information
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
TOC	Test of Cure (TOC)
TEAEs	Treatment emergent adverse events

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
T _{max}	Time to maximum concentration
VABP	Ventilator-associated bacterial pneumonia
VAP	Ventilator-associated pneumonia

Product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product name:</i>	Fetroja
<i>Active ingredient:</i>	Cefiderocol (as sulfate tosilate)
<i>Decision:</i>	Approved
<i>Approved therapeutic use for the current submission:</i>	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.
<i>Date of initial TGA decision:¹</i>	13 March 2026
<i>Date of final TGA decision:</i>	4 August 2026
<i>Date of entry onto ARTG:</i>	14 August 2026
<i>ARTG number:</i>	464691
<i>▼ Black Triangle Scheme</i>	Yes
<i>Sponsor's name and address:</i>	Accelagen Pty Ltd, Suite 2.02/785 Toorak Road, Hawthorn East, VIC, 3123, Australia.
<i>Dose form:</i>	Powder
<i>Strength:</i>	Each vial contains cefiderocol sulfate tosilate equivalent to 1 g of cefiderocol.
<i>Container:</i>	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.
<i>Pack size:</i>	10 vials.
<i>Route of administration:</i>	Intravenous infusion

¹ Following the initial decision the Sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act.

Dosage:	2 g of cefiderocol administered every 8 hours by intravenous 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. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Accelagen Pty Ltd (the Sponsor) to register Fetroja (cefiderocol as sulfate tosilate) for the following proposed indication:²

Treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options.

Disease or condition

The emergence of resistance to antibiotics has led to a reduction in the efficacy of existing antibiotics against various bacterial infections. Antibiotic resistance has been associated with high rates of mortality and morbidity. In 2019, antimicrobial resistance was linked to 4.95 million deaths, with one in five of these deaths occurring in children under the age of five.³ In 2020, Australia recorded 21663 infections and 1031 deaths associated with antimicrobial resistance in five separate pathogens (*Enterococcus* spp., *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Staphylococcus aureus*).⁴ This was despite a 9.2% reduction in antibiotic use within hospitals

² This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

³ Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–55

⁴ Wozniak TM, Dyda A, Merlo G, Hall L. Disease burden, associated mortality and economic impact of antimicrobial resistant infections in Australia. *Lancet Reg Health West Pac*. 2022 Jul 7;27:100521

between 2010 and 2015.⁵ There remains an unmet need to find a solution to address the global health challenge of increasing antibiotic resistance.

Current treatment options

Since 2017, thirteen new antibiotics and three new non-traditional antibiotics have been approved for marketing by foreign regulatory agencies around the world.⁶ Most of these agents are derivatives of known classes of antibiotics and have an indication for classic syndrome-based indications e.g. treatment of complicated intra-abdominal infection, community-associated bacterial pneumonia or hospital acquired pneumonia, and cUTIs. There remains a need for newer antibiotics that are sufficiently capable of treating the increasing antibiotic resistance present in Gram-negative bacteria including Enterobacterales, and non-fermenting bacteria such as *P. aeruginosa* and *A. baumannii*.

The 2024 World Health Organization (WHO) bacterial priority pathogen list (BPPL) identified a critical need for treatment options against carbapenem-resistant *A. baumannii*, third-generation cephalosporin-resistant Enterobacterales, and carbapenem-resistance Enterobacterales.⁶ Within the spectrum of new antibiotics introduced in the past 7 years, only two (one being cefiderocol) have shown activity against these critical priority pathogens. Five of the new antibiotics target one or more types of carbapenem-resistance Enterobacterales (with most data available for *E. coli* and *K. pneumoniae*), and seven are active against other high or medium priority pathogens from the WHO 2024 BPPL.

Table 1 lists the products that have been approved in Australia for the treatment of carbapenem-resistant Gram-negative bacterial infections.

Table 1. Antibiotics approved in Australia for the treatment of carbapenem-resistant Gram-negative bacterial infections.

Product	ARTG ID	Indication(s)
Zerbaxa (ceftolozane sulfate/tazobactam sodium)	229608	For the treatment of adult and paediatric (birth to less than 18 years of age) patients with the following infections caused by designated susceptible microorganisms: - Complicated intra-abdominal infections in combination with metronidazole - Complicated urinary tract infections, including pyelonephritis For the treatment of the following infection in adults (18 years or older): - Nosocomial pneumonia, including ventilator-associated pneumonia (VAP) Consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents.
Colistin Link (colistimethate sodium)	14667	For the treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli. It is particularly indicated when the infection is caused by

⁵ Department of Health and Aged Care 2023, [AMR and human health in Australia](#), Antimicrobial Resistance Portal, Australian Government.

⁶ [2023 Antibacterial agents in clinical and preclinical development: an overview and analysis](#). Geneva: World Health Organization; 2024.

Product	ARTG ID	Indication(s)
		sensitive strains of <i>Pseudomonas aeruginosa</i>. This antibiotic is not indicated for infections due to <i>Proteus</i> and <i>Neisseria</i>. Colistimethate sodium has proven clinically effective in treatment of infections due to the following gram-negative organisms: <i>Enterobacter aerogenes</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>. Pending results of appropriate bacteriologic cultures and sensitivity tests, colistimethate sodium may be used to initiate therapy in serious infections that are suspected due to gram-negative organisms.
Tygacil (tigecycline)	147450	For the treatment of the following infections in adults: - Complicated skin and skin structure infections, including those with methicillin resistant <i>Staphylococcus aureus</i> (MRSA), where there is suspected or proven resistance to, intolerance of, or there are co-morbidities preventing the use of, other available agents. - Complicated intra-abdominal infections, where there is suspected or proven resistance to, intolerance of, or there are co-morbidities preventing the use of, other available agents.
Zavicefta 2000/500 (ceftazidim/avibactam)	301205	For the treatment of the following infections in adults: - Complicated intra-abdominal infection in combination with metronidazole. - Complicated urinary tract infection including pyelonephritis. - Hospital-acquired pneumonia including ventilator associated pneumonia. For the treatment of the following infections in infants and paediatric patients (≥3 months to < 18 years) - Complicated intra-abdominal infection in combination with metronidazole - Complicated urinary tract infection including pyelonephritis Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Clinical rationale

Cefiderocol is proposed to meet the shortfall of antimicrobial agents that are sufficiently capable of treating life-threatening drug-resistant Gram-negative bacterial infections. It is potentially able to achieve this by overcoming three key resistance mechanisms exhibited by Gram-negative bacteria to β -lactam antibiotics: inactivation of the antibiotic by β -lactamase enzymes; reduced

outer membrane permeability as a result of porin channel mutations; and increased efflux of antibiotic from the periplasm due to overexpression of efflux pumps.

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, inhibiting bacterial peptidoglycan cell wall synthesis which leads to cell lysis and death.

Cefiderocol was designed to demonstrate bactericidal activity against carbapenem-resistant species of Gram-negative bacteria. It has a wide spectrum of antibacterial activity against aerobic Gram-negative bacteria including Enterobacterales (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and *Proteus* group) and glucose-nonfermenting bacteria (*P. aeruginosa*, *A. baumannii* complex, *B. cepacia* complex, and *S. maltophilia*).

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 2 summarises these submissions and provides the indications where approved.

Table 2. International regulatory status of Fetroja at the time of TGA submission.

Country	Date of submission	Date of approval or current status	Indication
United States	Initial NDA: 14 December 2018 Supplemental NDA: 27 March 2020	14 November 2019 (Treatment of Complicated Urinary Tract Infections) 25 September 2020 (Treatment of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia)	Treatment of the following infections caused by susceptible Gram-negative microorganisms: Complicated urinary tract infections (cUTI), including pyelonephritis. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)

Country	Date of submission	Date of approval or current status	Indication
European Economic Area (centralised)	4 March 2019	23 April 2020	Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
United Kingdom	4 March 2019	23 April 2020	Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Japan	24 March 2022	30 November 2023	Treatment of infections caused by cefiderocol-susceptible <i>Escherichia coli</i> , <i>Citrobacter</i> spp., <i>Klebsiella pneumoniae</i> , <i>Klebsiella</i> spp., <i>Enterobacter</i> spp., <i>Serratia marcescens</i> , <i>Proteus</i> spp., <i>Morganella morganii</i> , <i>Pseudomonas aeruginosa</i> , <i>Burkholderia</i> spp., <i>Stenotrophomonas maltophilia</i> , and <i>Acinetobacter</i> spp. (limited to bacterial strains resistant to carbapenem antimicrobial drugs).
Macau	18 December 2023	31 January 2024	Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Taiwan	12 December 2022	22 February 2024	Treatment of the following infections caused by susceptible Gram-negative microorganisms: Complicated Urinary Tract Infections (cUTI), including Pyelonephritis Hospital-acquired Bacterial Pneumonia and Ventilator-associated (HABP/VABP)
Republic of Korea	4 April 2023	NA	Treatment of the following infections caused by susceptible Gram-negative microorganisms: Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

Country	Date of submission	Date of approval or current status	Indication
			Hospital-acquired Bacterial Pneumonia and Ventilator-associated (HABP/VABP)
China	6 July 2024	NA	Treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i> , <i>Pseudomonas aeruginosa</i> and <i>Enterobacter cloacae</i> complex, <i>Acinetobacter baumannii</i> complex, <i>Citrobacter freundii</i> complex, <i>Klebsiella aerogenes</i> .

Registration timeline

Table 3 captures the key steps and dates for this submission.

Table 3. Registration timeline for Fetroja (cefiderocol as sulfate tosilate), submission PM-2024-04730-1-2

Description	Date
Submission dossier accepted evaluation commenced	2 December 2024
Evaluation completed	14 August 2025
Advisory committee meeting	4-5 December 2025
Registration decision (Outcome)	Approved
Registration in the ARTG completed	14 August 2026
Number of working days from submission dossier acceptance to registration decision*	252

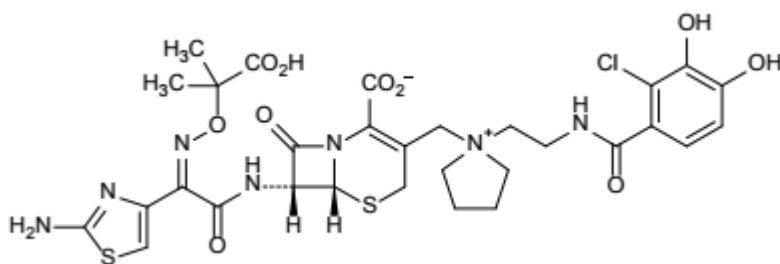
*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

Drug substance

Cefiderocol (Figure 1) is manufactured by chemical synthesis and possesses two chiral centres, both in the R configuration.

Figure 1. Chemical structure of cefiderocol

The drug substance is manufactured as a sulfate tosilate salt.

The drug substance is slightly to sparingly soluble in aqueous solutions from pH 1 – 11.

The proposed specification adequately controls the identity, potency, purity and chemical and physical properties of the drug substance relevant to the dose form.

The analytical methods used to analyse the product were adequately described and validated, and the data support the proposed retest period of 36 months when stored at -20°C, protected from light.

Drug product

Cefiderocol drug product is presented as a white to off white lyophilised powder for injection for intravenous infusion only, and is packaged in a 14 mL type I clear glass vial sealed with a chlorobutyl stopper, aluminium seal and a flip off cap. A pack size of 10 vials is proposed.

The drug product is reconstituted with 10 mL 0.9% sodium chloride or 5% dextrose solutions, and the volume after reconstitution is approx. 11.2 mL. The reconstituted solution is further diluted to 100 mL in the same solutions, and the recommended daily dose is 2 g every 8 hours, or 2 g every 6 hours for patients with increased renal clearance (8 g maximum daily dose).

The excipients are sucrose and sodium chloride, and the pH of the drug product bulk solution is adjusted with sodium hydroxide.

The drug product is reconstituted with 10 mL 0.9% sodium chloride or 5% dextrose solutions, and the volume after reconstitution is approx. 11.2 mL. The reconstituted solution is further diluted to 100 mL in the same solutions.

The drug product specifications adequately control the quality of the drug product at release and throughout the shelf-life.

A shelf life of 60 months stored at 2°C to 8°C, protected from light, is supported by the provided stability data.

Chemical and physical in-use stability has been demonstrated for 1 hour at 25°C after reconstitution, and after dilution 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. Sterility and endotoxin aspects were separately assessed by the TGA Laboratories Branch, and these were found to be acceptable.

No bioequivalence studies have been provided and are not required. The proposed 1 g/vial formulation was used in Phase 1, and Phase 3 clinical studies.

The Product Information is considered acceptable from a pharmaceutical quality perspective.

The labelling is considered acceptable from a pharmaceutical quality perspective.

The provisional ARTG records are finalised.

All manufacturing sites have valid GMP clearances.

There are no objections to registration from a pharmaceutical chemistry perspective.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals for human use (ICH M3(R2))⁷. The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.

Cefiderocol did not show significant secondary pharmacological activity against a panel of receptors, channels, or transporters.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory, and central nervous systems (CNS). No inhibition of hERG K⁺ channel tail current was observed at clinically relevant concentrations and no adverse effects were seen in cardiovascular systems in monkeys.

A low risk of QTc prolongation and associated cardiovascular events remain at the intended clinical dosing regimen. No CNS-related behavioural changes were associated with cefiderocol. Cefiderocol resulted in convulsions in rats at exposures similar to the clinical AUC in one repeat-dose toxicity study; in a different study however, no convulsions were observed in rats at moderate safety margins based on C_{max}. The potential risk of convulsive events occurring at the proposed clinical dosing regimen is considered low to moderate.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. cefiderocol was rapidly distributed in all species following intravenous administration. Half-life values were shorter in rat compared to monkeys and humans, while remaining broadly comparable. Plasma protein binding of cefiderocol sulfate tosylate was low to moderate in all animal species and humans. Tissue distribution of cefiderocol wide but penetration into brain and spinal cord was comparatively limited. Cefiderocol was mostly eliminated as unchanged parent compound in all species via urine and faeces (with urine as the predominant route in all species).

Cefiderocol inhibited CYP450 enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 at clinically relevant concentrations. Therefore, cefiderocol sulfate tosylate could affect the exposure of drugs which are metabolised by these enzymes. Cefiderocol also exhibited inhibitory activity against the renal transporters OAT1 and OAT3 indicating potential for clinically relevant interaction.

Repeat-dose toxicity studies by the intravenous route were conducted in rats (up to 3 months) and cynomolgus monkeys (up to 3 months). Maximum exposures (AUC) were low in both species. No target organs for toxicity were identified at exposure similar to the clinical AUC. An increase in kidney and liver weights were noted with no correlative toxicological histopathological findings, suggestive of an adaptive response.

Cefiderocol was not mutagenic in the bacterial mutation assay or the HPRT gene mutation test. No clastogenic potential was observed in the in vitro (human lymphocytes) or in vivo (the rat micronucleus test). No carcinogenicity studies were conducted, which is considered acceptable.

Fertility was unaffected in male and female rats treated with cefiderocol at exposure similar to the clinical AUC. No effect on embryofetal development was noted in rats or mice up to 1000 mg/kg/day and 2000 mg/kg/day, respectively, which is equivalent to the clinical exposure. In a pre-/post-natal development study in rats, no effects of cefiderocol were noted on reproductive

⁷ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. [ICH M3 \(R2\) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline](#). 2013.

function of the parent generation (F0) dams or the pre-/postnatal development of the next (F1) generation up to 1000 mg/kg/day (clinical AUC exposure). Distribution and excretion studies in rat revealed placental transfer of cefiderocol as well as excretion into milk.

Slight local irritation (chronic inflammation, thrombus formation and necrosis) was noted at the injection site in rat and monkey repeat dose studies. At formulation strengths comparable to the clinical formulation, lower incidence of irritation was observed in only the monkey study.

There were no objections to registration from a nonclinical perspective.

Clinical evaluation summary

Pharmacology

Pharmacokinetics

The Sponsor submitted eight clinical pharmacology studies in support of this application.

The pharmacokinetic (PK) data supported the approval of the application for cefiderocol.

Cefiderocol exhibits linear pharmacokinetics. Plasma concentration, $C_{\max}$ and AUC of cefiderocol were shown to increase in a dose-proportional manner following single doses ranging from 100 mg to 2000 mg, administered by intravenous infusion over 1 hour in healthy adult subjects (Study 1203R211).

The linear PK profile of cefiderocol was also demonstrated following administration of a single dose of cefiderocol at supratherapeutic doses (3 g and 4 g) (Study 1603R2116).

The terminal elimination half-life after a single 2 g dose of cefiderocol was 2.74 hours. The terminal elimination half-life at Day 10 after multiple doses of cefiderocol 2 g infused every 8 hourly was similar at 2.72 hours (Study 1203R211).

Following administration of cefiderocol at doses of 1 g and 2 g infused every 8 hourly in healthy adult subjects, $C_{\max}$ and AUC increased in a dose-proportional manner (Study 1203R211). Mean accumulation ratios (Day 10/Day 1) of $C_{\max}$ and AUC for each dose group were 1.07 and 1.05 at the 1 g dose, and 1.08 and 1.16 at the 2 g dose, respectively. Steady state was achieved within 1 day after the initiation of multiple doses.

Following administration of a single 1 g dose of [^{14}C]-cefiderocol infused over 1 hour, unchanged cefiderocol was the major radioactive component in plasma, accounting for 92.3% of the AUC_{0-16} for total radioactivity (Study 1516R2114). The major route of elimination was through urine (98.6%) with a minor route of elimination via faeces (2.8%). 90.6% of the administered dose was excreted as unchanged cefiderocol in urine. M2 was the main component identified in faeces, accounting for 1.7% of the administered dose.

After administration of a single dose of cefiderocol 2 g infused over 1 hour, the degree of penetration of cefiderocol into lung tissue (concentration ratio of epithelial lining fluid to plasma) ranged from 9.3% to 11.6% up to 6 hours post initiation of infusion (Study 1214R2112).

Following administration of multiple doses of cefiderocol 2 g every 8 hourly as a 3 hour infusion in conjunction with standard of care antibiotics in hospitalised patients with known or suspected bacterial pneumonia requiring mechanical ventilation, the degree of penetration of cefiderocol into lung tissue (concentration ratio of epithelial lining fluid to plasma) was 8.9% at 3 hours and 23.1% at 5 hours following the start of the infusion (Study 1713R2117).

Systemic exposure to cefiderocol was significantly increased in subjects with moderate, severe, and end-stage renal disease requiring haemodialysis relative to matched subjects with normal renal function (geometric mean [GM] ratio $AUC_{0-\infty} = 1.47, 2.55, \text{ and } 4.13$, respectively). No significant difference in exposure was observed between subjects with mild renal impairment and normal renal function (GM ratio $AUC_{0-\infty} = 1.03$, 90% CI: 0.82 - 1.29; Study 1222R2113).

Intermittent haemodialysis removed 62.3% of the total pool of cefiderocol.

The degree of renal impairment did not impact on plasma protein binding of cefiderocol. The unbound fraction of drug at 1- and 8-hours post initiation of infusion were comparable between renal function groups.

Cefiderocol did not significantly increase the $C_{\max}$ and AUC of furosemide (an OAT1 and OAT3 substrate), metformin (an OCT1, OCT2, and MATE2-K substrate) or midazolam (a CYP3A substrate). Cefiderocol increased the $C_{\max}$ and AUC of rosuvastatin (an OATP1B3 substrate) by 1.28-fold [90% CI: 1.12, 1.46] and 1.21-fold (90% CI: 1.08, 1.35), respectively (Study 1521R2115 and Study 2136R2118).

Population PK data

Population PK (PopPK) analysis was based on all available plasma cefiderocol concentration data pooled from 5 studies – phase 1 study in healthy adults (Study 1203R2111), phase 1 study in adults with impaired renal function (Study 1222R2113), phase 2 study (Study 1409R2121 [APEKS-cUTI]), phase 3 study (Study 1615R2132 [APEKS-NP]), and the pivotal phase 3 study (Study 1424R2131 [CREDIBLE-CR]). The analysis included 3427 plasma cefiderocol concentrations from 516 subjects.

The application included four popPK study reports: S-649266-CB-251-N, S-649266-CPK-004-B, S-649266-CPK-005-C and S-649266-CPK-007-C.

Based on popPK analysis, creatinine clearance had a significant and clinically meaningful effect on the clearance of cefiderocol. Other covariates including age, sex, race, body weight, albumin, infection site, and ventilation status did not have any clinically meaningful impact on the PK of cefiderocol.

The PopPK conclusions were aligned with those of foreign regulators. The adjusted dose regimen for renal function is approved in the US and EU.

Pharmacodynamics

Study 1603R2116 evaluated the effect of a single 2 g and 4 g dose of cefiderocol infused over 3 hours on the QT corrected using Fridericia's formula (QTcF) in healthy adult subjects.

It was concluded that administration of a single 2 g (therapeutic) and 4 g (supratherapeutic) dose of cefiderocol did not have a statistically or clinically significant effect in prolonging the QTc interval amongst healthy adult subjects. Changes in time-matched placebo- and baseline-adjusted HR, PR, and QRS were minimal, clinically insignificant and similar after administration of single 2 g or 4 g doses of cefiderocol.

Justification for dose selection

The proposed dose and dosage regimen was primarily developed based on PK/PD analyses of treatment of carbapenem-resistant infections in appropriate animal models and PopPK modelling.

The percentage of the dosing interval required for free-drug plasma concentration to exceed the minimum inhibitory concentration (MIC; %fT>MIC) was considered to be the key PK/PD index which best correlated with *in vivo* efficacy for cefiderocol. A target attainment for %fT>MIC of

75% was required for a 1- $\log_{10}$ bactericidal effect of cefiderocol in a neutropenic murine thigh infection model where infections were caused by Gram-negative bacteria, including carbapenem-resistant bacteria.

The MIC is the main variable that determines the %fT>MIC. In animal infection models, susceptibility to carbapenem-resistant Enterobacteriaceae, multidrug-resistant (MDR) *P. aeruginosa*, and MDR *A. baumannii* was observed at a MIC₉₀ ≤ 4 µg/mL.

It was shown that at a MIC of 4 µg/mL, intravenous infusion of cefiderocol 2 g every 8 hourly as 1- or 3-hour infusions would allow 90.7% and 99.9% of subjects, respectively, with normal renal function to attain a PK/PD target of 75% fT>MIC.

The European Medicines Agency's assessment of this application also highlighted 'the possible ability of cefiderocol to meet an unmet need i.e. treatment of carbapenem-resistant organisms expressing β -lactamases, particularly Ambler Class B or D enzymes, is based mainly on in-vitro data, on nonclinical efficacy data to determine PK/PD targets and on clinical PK data indicating that relevant PK/PD targets are met with the 2 g, 8 hourly, three times a day regimen when using 3h infusions. It is important to note that these data are pivotal to the application.'⁸

Adjustment for patients with renal impairment

The Sponsor's justification for dosage adjustment to account for impaired renal function and augmented renal clearance are acceptable from a PK point of view. The proposed dosage adjustments based on renal function are expected to provide adequate drug exposure in patients with renal impairment, augmented renal clearance and on continuous renal replacement therapy. There was a very high probability of attaining %fT>MIC of 75% using the proposed dose regimen in patients with normal or impaired renal function regardless of infection site.

It was also highlighted that although daily estimates of AUC were noted to be generally similar in patients who received cefiderocol that was dose adjusted based on renal function, the overall sample sizes in the severe renal impairment, end-stage renal disease, and continuous renal replacement therapy subgroups were very small.

Efficacy

Studies providing evaluable efficacy data included Study 1424R2131 (CREDIBLE-CR), Study 1615R2132 (APEKS-NP) and the phase 2 Study 1409R2121 (APEKS-cUTI).

An overview of these phase 2 and 3 clinical studies is shown in Table 4.

Table 4. Overview of cefiderocol phase 2 and 3 clinical studies

Study	Population	Total subjects exposed to cefiderocol	Treatment	Follow up
Phase 2				
1409R2121 APEKS-cUTI	Adult patients with cUTI (with or without pyelonephritis) or acute uncomplicated	448 (300)	Cefiderocol 2 g intravenously infused over 1	28 days following end of treatment.

⁸ European Medicines Agency. [Fetroja Assessment report](#) (2020).

Multicentre, double-blind, randomised	pyelonephritis caused by a Gram negative pathogen likely to be susceptible to Imipenem (IPM)		hour every 8 hours Comparator: Imipenem /cilastatin 1g IV administered every 8 hours as a 1 hour infusion	Total study duration 5-7 weeks for each patient.
Phase 3				
1424R2131 CREDIBLE-CR	Hospitalised adult patients with HAP/VAP/HCAP, cUTI, or BSI/sepsis caused by carbapenem resistant Gram negative pathogens	150 (101)	Cefiderocol 2 g intravenously infused over 3 hours every 8 hours	28 days following end of treatment. Total study duration 5-7 weeks for each patient.
APEKS-NP	Adult patients with HAP/VAP/HCAP caused by a suspected Gram negative pathogen	298 (148)	Cefiderocol 2 g intravenously infused over 3 hours every 8 hours	28 days following end of treatment. Total study duration 5-7 weeks for each patient.

APEKS-cUTI study

This was a phase 2, multicentre, double-blind, randomised, active-controlled, parallel-group study in subjects diagnosed with cUTIs with/without pyelonephritis or acute uncomplicated pyelonephritis. The study limited the percentage of subjects with acute uncomplicated pyelonephritis to no more than 30%.

Primary objective

The primary objective of the study was to compare the composite outcome of microbiological eradication and clinical response of cefiderocol with that of imipenem/cilastatin (IPM/CS) at Test of Cure (TOC) in subjects at risk of MDR Gram-negative pathogens originating from cUTIs with/without pyelonephritis or acute uncomplicated pyelonephritis.

Key secondary objectives

Secondary objectives compared clinical and microbiological responses to cefiderocol with IPM/CS at other timepoints (Early Assessment [EA], End of Treatment [EOT], and Follow-up [FU]); assessed microbiological responses per pathogen and per subject; and assessed clinical response per pathogen and per subject.

Inclusion criteria

Adults subjects (18 years and above) with symptomatic cUTI defined as a clinical syndrome characterised by pyuria and a documented or suspected microbial pathogen on urine or blood culture, accompanied by local and systemic signs and symptoms, including fever (i.e. temperature $\geq 38^{\circ}\text{C}$), chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness that (in the case of cUTI with or without pyelonephritis) occurred in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterisation and who required hospitalisation for intravenous treatment of cUTIs were enrolled in the study.

Subjects with a positive urine culture within 48 hours prior to randomisation which contained $\geq 10^5$ colony-forming units (CFUs)/mL of a Gram-negative uropathogens likely to be susceptible to imipenem were also eligible for the study. Subjects who had previously received and failed treatment with empiric antibiotics were eligible for the study if they had an identified Gram-negative uropathogen that was not susceptible to the previously used empiric treatment and likely to be susceptible to IPM.

Results

Table 5. Composite of clinical and microbiological outcome by time point - microbiological intent-to-treat population (Micro-ITT) population (Study 1409R2121)

Time Point	S-649266 (N = 252)	Imipenem/Cilastatin (N = 119)	Treatment Difference (%)	Comparison [a] 95% CI
Clinical and Microbiological Outcome	n (%)	n (%)		
Early Assessment				
Response	222 (88.1)	104 (87.4)	0.66	(-6.48, 7.79)
Failure	24 (9.5)	11 (9.2)		
Indeterminate	6 (2.4)	4 (3.4)		
End of Treatment				
Response	243 (96.4)	114 (95.8)	0.72	(-3.48, 4.92)
Failure	5 (2.0)	3 (2.5)		
Indeterminate	4 (1.6)	2 (1.7)		
Test of Cure				
Response	183 (72.6)	65 (54.6)	18.58	(8.23, 28.92)
Failure	54 (21.4)	46 (38.7)		
Indeterminate	15 (6.0)	8 (6.7)		
Follow-up				
Response	137 (54.4)	47 (39.5)	15.31	(4.69, 25.92)
Failure	92 (36.5)	49 (41.2)		
Indeterminate	23 (9.1)	23 (19.3)		

CI = confidence interval, IPM/CS = imipenem/cilastatin.

Percentage is calculated using the number of subjects in the column heading as the denominator.

[a] Treatment difference (S-649266 minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2- sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis).

At TOC, the composite of clinical and microbiological outcome was 72.6% (183/252 subjects) in the cefiderocol group and 54.6% (65/119 subjects) in the IPM/CS group, with an adjusted treatment difference (cefiderocol – IPM/CS) of 18.58% (95% CI: 8.23, 28.92). As the lower limit of the 95% CI was above the prespecified 20% margin, this demonstrated that the composite efficacy response for cefiderocol was noninferior to IPM/CS at TOC.

Sensitivity analysis undertaken in the microbiologically evaluable population at TOC yielded consistent results demonstrating noninferiority of cefiderocol to IPM/CS (treatment difference = 19.35% [95% CI; 8.87, 29.82]). Sensitivity analysis in the Micro-ITT population excluding subjects with indeterminate outcomes at TOC also yielded similar findings in favour of cefiderocol (treatment difference = 19.33% [95% CI; 8.91, 29.75]).

The design, conduct, and analysis of the study were generally acceptable.

For the primary efficacy endpoint of the composite of clinical and microbiological outcomes at TOC, cefiderocol was found to be noninferior to IPM/CS at the pre-specified noninferior margin of 20% (treatment difference = 18.58% [95% CI: 8.23, 28.92]). At FU, composite responses were attenuated in both treatment groups but still continued to favour the cefiderocol group overall (treatment difference = 15.31% [95% CI: 4.69, 25.92]).

Microbiological eradication rates (considered to be an objective measure) were consistent with those noted for the composite endpoint at TOC (treatment difference = 17.25% [95% CI: 6.92%, 27.58%]), with this response continuing to be sustained at FU (treatment difference = 13.92% [95% CI: 3.21, 24.63]). However, there was discordance with clinical outcomes at TOC, with both treatment groups having similar clinical response rates (cefiderocol: 89.7% (226/252 subjects); IPM/CS: 87.4% (104/119 subjects)).

The dose and dosage regimen for this study (cefiderocol, 2g IV, administered every 8 hours as a 1 hour infusion) differs from that proposed in this application (administration as a 3 hour infusion). Patients with carbapenem-resistant infections were excluded.

CREDIBLE-CR study

This was a phase 3, multicentre, global, open-label, parallel-group, randomised, active-controlled study. It was designed to evaluate the efficacy of cefiderocol in the treatment of serious infections caused by a range of carbapenem-resistant Gram-negative bacterial infections including, but not limited to, carbapenem-resistant Enterobacteriaceae and carbapenem-resistant non-fermenters, such as carbapenem-resistant *P. aeruginosa*, and carbapenem-resistant *A. baumannii*. Target pathogens did not include Gram-positive or anaerobic bacteria.

Primary objectives

- To assess at TOC, the clinical outcome of treatment with cefiderocol or best available therapy (BAT) in adult subjects with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infection (BSI)/sepsis caused by carbapenem-resistant Gram-negative pathogens.
- To assess at TOC, the microbiological outcome of treatment with cefiderocol or BAT in adult subjects with cUTIs caused by carbapenem-resistant Gram-negative pathogens.

Key secondary objectives

The secondary objective of the study was to assess the safety of cefiderocol.

Inclusion criteria

Hospitalised adult subjects (18 years of age or older) with clinically documented infection (HAP/VAP/HCAP, cUTI, or BSI/sepsis) caused by a Gram-negative pathogens with evidence of carbapenem resistance were eligible for inclusion in the study.

Initial evidence of carbapenem-resistant Gram-negative bacterial pathogens could be derived from 1) rapid diagnostic tests; 2) failed empiric treatment where the target pathogen was identified as a carbapenem-resistant Gram-negative bacterial pathogen; 3) identified infection with *Stenotrophomonas maltophilia* (due to inherent carbapenem resistance); 4) current

hospital antibiogram for Gram-negative bacteria showing a carbapenem resistance rate of > 90%; or 5) subject who was known to be colonised with carbapenem-resistant Gram-negative pathogen(s) prior to developing the acute infection.

Results for the primary efficacy outcome

For subjects with HAP/VAP/HCAP or BSI/sepsis, clinical cure rates were comparable between the two treatment groups. For subjects with cUTI, the cefiderocol group had a higher microbiological eradication rate at TOC compared to the BAT group, however these conclusions are somewhat limited by the small sample size and relatively high number of indeterminate outcomes in the BAT group (3/5 subjects [60.0%]).

Sensitivity analysis of the primary efficacy endpoint using the Carbapenem-resistant Microbiologically Evaluable population, Micro-ITT, and Carbapenem-resistant Microbiological Intent-to-treat population 2 (clinical outcome only) populations were comparable to that of the primary efficacy analysis.

Table 6. Primary efficacy outcomes by infection site at TOC - carbapenem-resistant microbiological intent-to-treat (CR Micro-ITT) population (Study 1424R2131)

Endpoint	Infection site	Cefiderocol (%)	BAT (%)
Clinical Cure	HAP/VAP/HCAP	50.0 (20/40) [33.8, 66.2]	52.6 (10/19) [28.9, 75.6]
	BSI/sepsis	43.5 (10/23) [23.2, 65.5]	42.9 (6/14) [17.7, 71.1]
Microbiological eradication	cUTI	52.9 (9/17) [27.8, 77.0]	20.0 (1/5) [0.5, 71.6]

BAT = best available therapy; BSI = bloodstream infection; CI = confidence interval; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Percentage was calculated using N' as the denominator where N' is the number of subjects who had the specified infection site. The 95% CI was calculated using Clopper-Pearson method.

Eradication is defined as urine culture shows the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL are reduced to $< 10^3$ CFU/mL.

Other efficacy outcomes

At other time points, for subjects with HAP/VAP/HCAP, clinical response rates remained comparable at EOT, and was higher in the cefiderocol group compared to the BAT group at FU. For subjects with BSI/sepsis, clinical response rates at EOT and FU tended to be higher in the cefiderocol group compared to the BAT group. For subjects with cUTI, clinical response rates were higher in the cefiderocol group compared to the BAT group at EOT and TOC, and lower at FU.

When all infection sites were combined, clinical response rates were similar at EOT and TOC between the treatment arms, whilst sustained cure rates tended to be higher in the cefiderocol group compared to the BAT group at FU. At TOC, clinical cure rates amongst subjects with *A. baumannii* isolated at baseline was lower in the cefiderocol group compared to the BAT group whilst for *K. pneumoniae*, the opposite was true. For subjects isolated with *P. aeruginosa*, clinical cure rates were similar.

When all infection sites were combined, microbiological eradication rates at TOC and FU were generally higher in the cefiderocol group compared to the BAT group. However, eradication rates were noted to be relatively low in both treatment arms (~20.0 - 30.0%). At TOC, the eradication rate of *A. baumannii* and *P. aeruginosa* were comparable between the two groups,

whilst for *K. pneumoniae*, it was noted to be higher in the cefiderocol group compared to the BAT group.'

The high rate of discontinuation from the study within both the cefiderocol and BAT treatment groups (31.7% vs 25.5%) was noted.

The analysis undertaken per Gram-negative pathogen are largely only applicable to *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*, as these were the most frequently isolated pathogens at baseline for all infection sites combined. Other pathogens were isolated at baseline in much lower frequencies and meaningful conclusion cannot be drawn regarding the efficacy of cefiderocol in these bacterial species.

Study 1615R2132 (APEKS-NP)

This was a phase 3, multicentre, multinational, double-blind, parallel-group, randomised, active-controlled study in ~ 300 subjects with documented nosocomial pneumonia caused by Gram-negative bacteria. The study was designed to demonstrate that cefiderocol is noninferior to high-dose meropenem in the treatment of subjects with HAP, ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens.

Primary objective

The primary objective was to compare the all-cause mortality at Day 14 in subjects who received cefiderocol to subjects who received meropenem, in adults with HAP, VABP, or HCABP caused by Gram-negative pathogens.

Key secondary objectives were:

- To compare the microbiological outcome of treatment with cefiderocol with meropenem at TOC.
- To compare the clinical outcome of treatment with cefiderocol with meropenem in subjects at TOC.
- To compare all-cause mortality at Day 14 of cefiderocol with meropenem with regards to superiority of cefiderocol.

Other secondary efficacy objectives compared clinical and microbiological outcomes of treatment at other timepoints (EA, EOT, and FU) and compared all-cause mortality at Day 28 and End of Study.

Inclusion criteria

Adult subjects (18 years or older) who had a clinical diagnosis of HAP, VABP, HCABP caused by an aerobic Gram-negative pathogen only or in combination with an aerobic Gram-positive or anaerobic pathogen who required hospitalisation for parenteral treatment of the infection.

The test product was cefiderocol 2 g, administered IV every 8 hourly as a 3-hour infusion in subjects with normal renal function. The comparator was meropenem 2 g administered IV every 8 hourly as a 3-hour infusion in subjects with normal renal function.

Linezolid 600 mg, administered intravenously every 12 hours over 30 minutes to 2 hours was given concomitantly for at least 5 days to provide coverage for Gram-positive bacteria in the cefiderocol arm, to provide coverage for methicillin resistant *Staphylococcus aureus* in both study arms, and to maintain the study blind.

Results for the primary efficacy outcome

All-cause mortality at Day 14 was 12.4% (18/145 subjects) in the cefiderocol group and 11.6% (17/146 subjects) in the meropenem group (Table 7). The difference in all-cause mortality between the two groups (cefiderocol – meropenem) was 0.8% (95% CI: -6.6, 8.2). As the upper limit of the 95% CI was < 12.5%, cefiderocol therefore demonstrated noninferiority to meropenem and the primary efficacy endpoint was met. Noninferiority continued to be demonstrated in sensitivity analysis undertaken in the Intent-to-Treat population and Micro-evaluable Per-Protocol population.

Table 7. All-cause mortality rate at Day 14 - Modified intent-to-treat (mITT) population (Study 1615R2132)

Survival Status	Cefiderocol (N = 145) n/N' (%)	Meropenem (N = 147) n/N' (%)	Total (N = 292) n/N' (%)	Treatment Comparison [a]		
				Difference (%)	95% CI [b]	p-value
Day 14 ACM	18/145 (12.4)	17/146 (11.6)	35/291 (12.0)	0.8	(-6.6, 8.2)	0.0020[c]

CI = confidence interval; Day 14 ACM = all-cause mortality at Day 14 since the first infusion of study treatment; N = number of subjects in the analysis set; n = number of subjects who died; N' = number of subjects with known survival status.

[a] Treatment difference (cefiderocol minus meropenem) was the adjusted estimate of the difference in the ACM rate at Day 14 between the 2 treatment arms based on Cochran-Mantel Haenszel weights using Acute Physiology and Chronic Health Evaluation II score (≤ 15 and ≥ 16) as the stratification factor.

[b] The 95% CI (2-sided) was based on a stratified analysis using Cochran-Mantel Haenszel weights using Acute Physiology and Chronic Health Evaluation II score (≤ 15 and ≥ 16) as the stratification factor. The CI was calculated using a normal approximation to the difference between 2 binomial proportions (Wald method).

[c] p-value for noninferiority hypothesis.

Key secondary endpoints

Microbiological outcome at test of cure

The microbiological eradication rate at TOC in the Modified intent-to-treat (mITT) population was 47.6% (59/124 subjects) in the cefiderocol group and 48.0% (61/127 subjects) in the meropenem group for a difference of -1.4% (95% CI: -13.5, 10.7). In subjects who were not susceptible to meropenem, eradication rates at TOC were higher in subjects treated with cefiderocol compared to meropenem (40.0% vs 33.3%, respectively). No difference in eradication rate was noted between the groups where subjects were susceptible to meropenem (50.0% in both groups).

Clinical outcome at test of cure

The clinical cure rate at TOC in the mITT population was 64.8% (94/145 subjects) in the cefiderocol group and 66.7% (98/147 subjects) in the meropenem group, for a difference of -2.0% (95% CI: -12.5, 8.5). As the criteria for multiplicity were not met, this endpoint was not tested for statistical significance. Clinical cure rates at TOC remained similar between the cefiderocol and meropenem group regardless of baseline meropenem susceptibility status.

The study design, conduct, and analysis were generally acceptable. The study demonstrated that for the primary efficacy outcome of all-cause mortality at Day 14, cefiderocol was noninferior to high dose meropenem (treatment difference = 0.8% [95% CI: -6.6, 8.2] at the noninferiority margin of 12.5%. All-cause mortality continued to be similar between the two treatment groups up to Day 28 and End of Study. For the key secondary efficacy endpoints, both microbiological eradication at TOC and clinical cure rate at TOC were noted to be similar between the cefiderocol and meropenem groups.

A relatively large proportion of subjects in both treatment groups discontinued from the study (28.4% and 26.3% in the cefiderocol and meropenem groups, respectively), with death being the most common reason for discontinuation (26.4% and 22.4%, respectively).

In their assessment of this application, the EMA highlighted that this study was requested to be submitted to the EMA due to the imbalance in mortality noted in the interim analysis of the CREDIBLE-CR study in the subset of subjects with HAP/VAP/HCAP at the time.

Safety

Clinical trials

Across the 3 clinical studies, cefiderocol was generally found to be well tolerated. Approximately two thirds of the cefiderocol group in the CREDIBLE-CR and APEKS-NP studies received cefiderocol for the recommended duration of 7 to 14 days. In the APEKS-cUTI, 92.3% of subjects who received cefiderocol had exposure to study treatment for the recommended duration of 7 to 14 days. Across the 3 studies, a total of 549 subjects were exposed to cefiderocol, of which only 248 received cefiderocol at the proposed dosage regime of 2 g every 8 hourly over a 3-hour infusion period (300 received the same dose over a 1-hour infusion period). An additional 233 subjects were exposed to cefiderocol in the clinical pharmacology studies.

Although the overall number of subjects exposed to cefiderocol is considered to be relatively low, it is appreciated that attaining high subject numbers may have been difficult in the context of a heterogeneous patient population experiencing serious, life threatening conditions and the challenges associated with recruiting subjects from this population that met the eligibility criteria of the studies.

The incidence of treatment-related adverse events (AEs) tended to be lower in the cefiderocol group compared to the corresponding comparator group in each of the clinical studies:

- CREDIBLE-CR (14.9% for cefiderocol vs 22.4% for BAT).
- APEKS-NP (9.5% for cefiderocol vs 11.3% for meropenem).
- APEKS-cUTI (9.0% for the cefiderocol vs 11.5% for IPM/CS).

The imbalance in mortality in the CREDIBLE-CR study was noted. In the CREDIBLE-CR study, there was a higher incidence of subjects with AEs with an outcome of death in the cefiderocol group compared to the BAT group (33.7% vs 18.4%, respectively). However, none of the deaths in the cefiderocol group were considered treatment-related. All-cause mortality was noted to be higher in the cefiderocol group compared to the BAT group up to the end of the study.

Specifically, there was a higher all-cause mortality amongst subjects who had *Acinetobacter* infection in the cefiderocol group compared to the BAT group. Although the cause of this was not clear, the higher frequency of shock and admission in ICU amongst subjects with *Acinetobacter* infection in the cefiderocol group may have been a contributory factor. In the APEKS-NP study, the percentage of subjects with AEs that led to death were similar between the cefiderocol and meropenem treatment arms (26.4% and 23.3%, respectively).

In the cefiderocol group, there was one subject who had a treatment-related serious adverse event leading to death. There was a single death in the APEKS-cUTI study, occurring in a subject who received cefiderocol and was attributed to non treatment-related cardiorespiratory arrest.

Adverse events of special interest

AEs of interests included antibiotic-related AEs (*C. difficile*-related AEs and diarrhoea) and cephalosporin class specific effects (hepatic related AEs, rash/hypersensitivity reactions,

seizures, and bone marrow suppression). Three new safety signals have been identified in the post marketing periods since May 2021: chromaturia, neutropenia and eosinophilia.

Risk of antimicrobial resistance

Emergence of resistance was determined by assessing for at least a 4-fold increase in MIC from baseline per pathogen. In the CREDIBLE-CR study, a total of 15 patients met these criteria.

Three of these subjects had Gram-negative pathogens where the maximum postbaseline MIC was $> 4 \mu\text{g/mL}$ (1 subject with *A. baumannii* with postbaseline MIC of $8 \mu\text{g/mL}$, 2 subjects with *A. baumannii* with postbaseline MICs of $>64 \mu\text{g/mL}$). In the APEKS-NP study, a total of 9 patients had Gram-negative pathogens with a ≥ 4 -fold increase in MIC from baseline. One of these subjects had isolates with maximum postbaseline MIC $> 4 \mu\text{g/mL}$ (1 subject with *K. pneumoniae* with a MIC of $8 \mu\text{g/mL}$). In the APEKS-cUTI study, 7 subjects in the cefiderocol group were noted to have ≥ 4 -fold increase in MIC from baseline during the study (3 *E. coli*, 1 *P. mirabilis*, 1 *E. cloacae* complex, 1 *E. aerogenes*, 1 *P. aeruginosa*), although no strains exceeded a MIC of $4 \mu\text{g/mL}$.

Based on this evidence from the clinical studies, it is determined that there is a low but potential risk of development of antibiotic resistance to cefiderocol.

In the post market setting (from 14 November 2020 to 13 May 2021), a total of 17 AEs related to antibiotic resistance to cefiderocol were reported in 16 patients. This included 7 events of 'treatment failure', 7 events of 'pathogen resistance' and 3 events of 'drug ineffective'. Amongst the 7 events of 'pathogen resistance', pathogens included *A. baumannii*, *K. pneumoniae*, *P. aeruginosa* and *E. coli*. The remaining cases of 'treatment failure' and 'drug ineffective' were not considered to be related to antibiotic resistance development.

The Sponsor advised that no signals or safety concerns for the development of antibiotic resistance with cefiderocol have been detected based on cumulative data from over 666,000 patient-days up to 13 November 2024. In the post marketing period from 14 November 2019 (international birth date) to 13 November 2024, 24 cases of the preferred term "Pathogen resistance" and 100 cases of the preferred term "drug resistance" were identified. None of these cases clearly suggested development of cefiderocol resistance causing serious outcomes.

Additionally, no new signals regarding antibiotic resistance with cefiderocol were identified in the global antimicrobial surveillance program (SENTRY) conducted in post marketing period.

Real world data

Real world data were included in this submission included a compassionate use report and a PSUR for the interval 14 November 2020 to 13 May 2021. Further post-marketing data up to November 2024 were provided upon request. These data were considered supportive to the application.

Risk management plan

Accelagen Pty Ltd has submitted EU-RMP version 1.0 (dated 31 March 2020; DLP 24 December 2019) and ASA version 0.1 (dated 8 October 2024) in support of this application.

In response to section 31 response, the Sponsor provided ASA version 0.2 dated 24 June 2025 corresponding to EU-RMP version 1.0 (dated 31 March 2020; DLP 24 December 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 8. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	-	-	-	-
Important potential risks	Antibiotic resistance development	✓	-	✓	-
Missing information		-	-	-	-

Recommendation following the clinical evaluation

At the end of the evaluation phase, the TGA was inclined to approve the registration of Petroja for the following indication:

Petroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Following the delegate's overview the TGA requested that the indication be more specific, consistent with the FDA indication, with the final wording to be confirmed following deliberations at the Advisory Committee on Medicines (ACM) meeting:

Petroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with:

Complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Enterobacter cloacae complex.

Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens.

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

Risk-benefit analysis

The TGA is of the opinion that registration of Petroja can be recommended. Limitations of the data are acknowledged and include the limited exposure in the target population. The Delegate concurs with the clinical evaluator that size of the safety database was limited by difficulties in recruiting from a heterogenous population with serious, life-threatening illnesses. Ongoing post-market data will be accumulated and the safety data provided to date are consistent with class effects for cephalosporins.

The increase in mortality noted in the CREDIBLE-CR study amongst subjects who had Acinetobacter infection in the cefiderocol group compared to the best available therapy group

warrants further discussion, acknowledging that subsequent studies have not identified this signal and that the sample size for the CREDIBLE-CR study was limited.

The pivotal studies for the development program for Fetroja have undergone considerable input from overseas regulators, including the FDA and EMA, and the Delegate acknowledges that more treatment options are needed for patients with life-threatening drug-resistant Gram-negative bacterial infections.

Advice from the Advisory Committee on Medicines was sought.

Advisory Committee considerations

The [Advisory Committee on Medicines \(ACM\)](#), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

1. *The ACM is requested to comment on the Delegate's proposed wording of the indication for Australia, considering the submitted data, overseas status of Fetroja and the indications for similar agents approved in Australia for the treatment of carbapenem-resistant Gram-negative bacterial infections.*

The ACM noted differences in international indications for Fetroja. These could be broadly divided into pathogen-specific and site-specific indications. The ACM also took into consideration the:

- approved indications for similar antibiotics in Australia, which were generally site-specific
- guidance in the TGA-adopted guideline CPMP/EWP/558/95R3
- population studied in the pivotal trial CREDIBLE-CR which were hospitalised adults with site-specific infections caused by carbapenem-resistant Gram-negative pathogens
- populations studied in both the APEK-cUTI and APEKS-NP studies which the ACM noted as clearly informing the indication, despite not being described as pivotal in the Clinical Evaluation Report.

The ACM advised there was insufficient data to support the inclusion of blood stream infections/sepsis in the proposed wording of the indication. In addition, the ACM considered that the development of resistance to Fetroja is a significant and important future risk.

The ACM concluded that a site-specific approach allows for sufficient flexibility in prescribing for critically ill patients, with the addition of key phrases (as per the proposed indication in the ACM conclusion below) to mitigate the future risk of resistance. This is supported by TGA-guidelines, in keeping with the precedence set by previous approvals, and clinical trial evidence submitted by the Sponsor.

2. *Related to question 1, should the indication for Australia specify the micro-organisms to which Fetroja is susceptible in vitro or to which Fetroja demonstrated efficacy in the clinical trials, acknowledging there is some discordance between these groups? Should the indication specify the site of infection, noting that evidence of efficacy was most compelling for the HAP/VAP/HCAP indications and cUTI including pyelonephritis?*

The ACM discussed benefits and risks of a pathogen-specific and site-specific approach to indication. A pathogen-specific approach may be considered limiting to clinicians. All possibly susceptible organisms were not encountered in the clinical trials, and physicians may need to use Fetroja in a context where there is a lack of data.

The TGA-adopted guidance document ([CPMP/EWP/558/95 rev 2](#)) was reviewed, and the ACM noted that the stated requirement for indication based on clinical syndrome/population. The ACM also noted that pathogen-only indications are rare.

The ACM was satisfied that a site-specific approach to the indication was generally supported by the data presented. Additionally, the ACM advised that a site-specific approach would allow for sufficient flexibility in prescribing for critically ill patients. However, it was noted that there was insufficient data to support the use of Fetroja in blood stream infections/sepsis.

The ACM acknowledged that a site-specific indication may be more restrictive compared to an organism-specific approach. However, the ACM noted that this restriction was appropriate under the principles of antimicrobial stewardship. Further, the ACM advised that Fetroja would most likely be used by specialist physicians which would further alleviate any concerns regarding potential restrictions. The ACM advised that a statement noting microbiological spectrum of activity, clinical data and special warnings should be added to the indication to direct clinicians to appropriate data presented elsewhere in the PI.

The ACM advised that the wording of: “proven or strongly suspected carbapenem-resistance” should be included in the indication. It was also recommended that the following phrase be added: “It is recommended that Fetroja should be used after consultation with a physician with appropriate experience in the management of infectious diseases.”

The ACM discussed whether the phrase “limited treatment options” was sufficiently clear for inclusion in the indication. The ACM held the view that the phrase implies that Fetroja is a second line antibiotic to be used after other suitable options have been considered. This was considered subtle but important to keep in the PI, so that Fetroja is not considered a first line option, thereby mitigating the risk of future antibiotic resistance.

Overall, the ACM advised that the indication should include the site of infection and does not require the specific susceptible organism. Blood stream infections/sepsis should be excluded from the indication due to a lack of data.

3. *A higher all-cause mortality was observed in the CREDIBLE-CR study amongst subjects who had Acinetobacter infection in the cefiderocol group compared to the best available therapy (BAT) group. Does the ACM have further comments on these results and the information to be included in the proposed PI? Please also see the question to the Sponsor.*

The ACM was satisfied that the elevated all-cause mortality rates seen in the Acinetobacter subgroup of the CREDIBLE-CR study was unlikely to be related to Fetroja treatment.

However, the ACM advised that this data, including the subgroup analysis be included in the PI.

4. *Are the submitted data sufficient to reach conclusions regarding the safety of Fetroja, acknowledging the limited number of participants in clinical trials and reliance on in vitro and PK data?*

The ACM agreed the safety data was sufficient to support approval. The ACM further advised that evidence supported Fetroja’s positive safety profile, citing considerable clinician experience with the cephalosporin class of antibiotics and ongoing post-marketing data from other jurisdictions.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the initial TGA-approved indication as worded below:

“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 spectrum of activity of cefiderocol and clinical data (section 5.1) and special warnings (section 4.4):

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.”

Section 60 review and outcome

Following the initial decision to approve cefiderocol (as sulfate tosilate) on the ARTG for the initial TGA approved indication, on 10 June and 11 June 2026, the Sponsor sought a review under the provisions of section 60 of the Act.

The initial TGA-approved indication was as follows:

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. **(TGA Approved Indication)***

In their request for reconsideration, the applicant proposed a revised version of the Initial Indication, termed the Proposed Indication) in addition to an Alternative Indication to be considered by the TGA if the revised version was found to be unfavourable:

Proposed indication:

Fetroja is indicated for the treatment of infections due to 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)

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.

Alternative indication:

Fetroja is indicated for the treatment of infections due to 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

- Bloodstream infections.

Fetroja is also indicated for the treatment of infections due to Gram-negative organisms in adults with limited treatment options.

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.

The quality, safety and efficacy of a medicine must be satisfactorily established for the purpose for which it is proposed to be used (as set out in the indication proposed by the Applicant and PI) in order for it to be registered. After evaluation of the information provided, the Delegate found that efficacy is not established for the breadth of the patient population captured by the applicant's Proposed Indication for infections due to aerobic Gram-negative organisms in adults with limited treatment options. Accordingly, the Delegate did not register the Medicine in respect to the Proposed Indication.

While the Delegate found that on balance, safety and efficacy are satisfactorily established for patients with hospital-acquired and healthcare associated sepsis, the Applicant's Alternative Indication relates to a broader population of patients with bloodstream infections. The Delegate found that efficacy is not established for patients with sepsis outside of those with hospital-acquired and healthcare associated aerobic Gram-negative organisms in adults with limited treatment options. Further to this, the Alternative Indication also includes the phrase '*Fetroja is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options....*' As stated above, the Delegate found that efficacy is not established for the breadth of the patient population captured by this proposed intended use. Accordingly, the Delegate did not register the Medicine in respect to the Alternative Indication.

The Delegate found that safety and efficacy are established for patients with infections due to proven or strongly suspected carbapenem-resistant aerobic Gram-negative organisms in adults with limited treatment options: cUTIs, including pyelonephritis, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Consequently, the Medicine can be registered for the TGA Approved Indication. Accordingly, the Delegate confirmed the initial decision to approve the registration of the Medicine. On 4 August 2026, a delegate of the Minister confirmed the initial decision to approve the TGA Approved Indication of the medicine.

The TGA's decision to confirm the initial decision to register the medicine was reviewable by the Administrative Review Tribunal pursuant to subsection 60(8) of the Act.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Fetroja (cefiderocol as sulfate tosilate) for the following indication:

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.

Specific conditions of registration

Fetroja (cefiderocol sulfate tosilate) is to be included in the Black Triangle Scheme. The PI and CMI for Fetroja must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The Fetroja EU-Risk Management Plan (RMP) (version 1.0, dated 31 March 2020, data lock point 24 December 2019), with Australia-Specific Annex (ASA) (version 0.2, dated 24 June 2025), included with submission PM-2024-04730-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA [PI/CMI search facility](#).

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