

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Fetroja 1 g powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

Each vial contains 7.64 mmol of sodium (approximately 176 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fetroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections 4.2, 4.4 and 5.1).

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

4.2 Posology and method of administration

It is recommended that Fetroja should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Posology

Table 1 Recommended dose of Fetroja¹ for patients with a creatinine clearance (CrCL) ≥ 90 mL/min²

Renal function	Dose	Frequency	Duration of treatment
Normal renal function (CrCL ≥ 90 to < 120 mL/min)	2 g	Every 8 hours	Duration in accordance with the site of infection ³
Augmented renal clearance (CrCL ≥ 120 mL/min)	2 g	Every 6 hours	Duration in accordance with the site of infection ³

¹To be used in combination with antibacterial agents active against anaerobic pathogens and/or Gram-positive

pathogens when these are known or suspected to be contributing to the infectious process.

²As calculated using the Cockcroft-Gault formula.

³e.g. for complicated urinary tract infections including pyelonephritis and complicated intra-abdominal infections the recommended treatment duration is 5 to 10 days. For hospital-acquired pneumonia including ventilator-associated pneumonia the recommended treatment duration is 7 to 14 days. Treatment up to 21 days may be required.

Special populations

Renal impairment

Table 2 Recommended dose of Fetroja for patients with a CrCl < 90 ml/min¹

Renal function	Dose	Frequency
Mild renal impairment (CrCL \geq 60 to < 90 mL/min)	2 g	Every 8 hours
Moderate renal impairment (CrCL \geq 30 to < 60 mL/min)	1.5 g	Every 8 hours
Severe renal impairment (CrCL \geq 15 to < 30 mL/min)	1 g	Every 8 hours
End stage renal disease (CrCL < 15 mL/min)	0.75 g	Every 12 hours
Patient with intermittent haemodialysis ²	0.75 g	Every 12 hours

¹As calculated using the Cockcroft-Gault formula.

²As cefiderocol is removed by haemodialysis, administer cefiderocol at the earliest possible time after completion of haemodialysis on haemodialysis days.

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Elderly population

No dosage adjustment is required (see section 5.2).

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.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Hypersensitivity to any cephalosporin antibacterial medicinal product.

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

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity has been reported with cefiderocol (see sections 4.3 and 4.8).

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 Fetcroja, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics (see section 4.3).

If a severe allergic reaction occurs, treatment with Fetcroja 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 (see section 4.8). 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 cefiderocol. Discontinuation of therapy with cefiderocol and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizure

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 cefiderocol should be adjusted based on renal function (see section 4.2). Alternatively, cefiderocol should be discontinued.

Limitations of the clinical data

In clinical trials, cefiderocol 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 cefiderocol 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 randomized clinical trial in which 80 patients were treated with Fetcroja and 38 patients were treated with best available therapy for infections caused by carbapenem-resistant organisms.

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

A higher all-cause mortality rate was observed in patients treated with cefiderocol as compared to best available therapy (BAT) in a randomised, open-label trial in critically-ill patients with infections known or suspected to be due to carbapenem-resistant Gram-negative bacteria. The higher day 28 all-cause mortality rate with cefiderocol occurred in patients treated for nosocomial pneumonia, bacteraemia and/or sepsis [25/101 (24.8%) vs. 9/49 (18.4%) with BAT; treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with cefiderocol through end-of-study [34/101 (33.7%) vs. 9/49 (18.4%) with BAT; treatment difference 15.3%, 95% CI (-0.2, 28.6)]. The cause of the increase in mortality has not been established. In the cefiderocol group there

was an association between mortality and infection with *Acinetobacter spp.*, which accounted for the majority of infections due to non-fermenters. In contrast, mortality was not higher in cefiderocol vs. BAT patients with infections due to other non-fermenters.

Spectrum of activity of cefiderocol

Cefiderocol has little or no activity against the majority of Gram-positive organisms and anaerobes (see section 5.1). Additional antibacterial medicinal products should be used when these pathogens are known or suspected to be contributing to the infectious process.

Non-susceptible organisms

The use of cefiderocol may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.

Renal function monitoring

Renal function should be monitored regularly as dose adjustment may be needed during the course of therapy.

Drug/laboratory test interactions

Cefiderocol may result in false-positive results in urine dipstick tests (urine protein, ketones, or occult blood). Alternative methods of testing should be used by the clinical laboratories to confirm positive tests.

Antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with cefiderocol.

Controlled sodium diet

Each 1 g vial contains 7.64 mmol of sodium (approximately 176 mg).

Each 2 g dose of cefiderocol, when reconstituted with 100 mL of 0.9% sodium chloride injection, provides 30.67 mmol (705 mg) of sodium and is approximately 35% of the WHO adult recommended maximum daily dietary intake. The total daily dose (2 g administered 3 times a day) of sodium from cefiderocol therapy is 2.1 g, just greater than the WHO recommend daily maximum of 2 g sodium for an adult.

When reconstituted in 100 mL of 5% dextrose injection each 2 g dose of cefiderocol provides 15.28 mmol (352 mg) of sodium. The total daily sodium dose (2 g administered 3 times a day) from cefiderocol reconstituted in 5% dextrose injection is 1,056 mg which is approximately 53% of the WHO adult recommended maximum daily dietary intake of 2 g sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Cefiderocol induces CYP3A4 *in vitro*. Therefore, the metabolism of co-administered medicinal products that are substrates of CYP3A4 is expected to increase and lead to decreased systemic exposure of these medicinal products. If cefiderocol is administered together with substrates of CYP3A4, the patients should be monitored for decreased efficacy of the concomitant drug. The effect of systemic hormonal contraceptives may be reduced; thus it is recommended to use an additional contraceptive method during and until 28 days after treatment with cefiderocol.

As the *in vitro* CYP3A4 induction by cefiderocol is PXR mediated, other PXR inducible proteins may also be induced, for example the CYP2C family and P-gp. The clinical relevance of this induction is

unknown. As a consequence, if cefiderocol is administered together with substrates of the CYP2C family or P-gp, the patients should be monitored for decreased efficacy of the concomitant drug.

Based on *in vitro* studies and one phase 1 clinical evaluation no significant drug-drug interactions are anticipated between cefiderocol and substrates or inhibitors of cytochrome P450 enzymes (CYPs) or transporters (see section 5.2), except for the above mentioned induction of CYP3A4, CYP2C and P-gp.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of cefiderocol sodium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Fetcroja during pregnancy.

Breast-feeding

It is unknown whether Fetcroja/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fetcroja therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of cefiderocol on fertility in humans has not been studied. Based on preclinical data, from a study with sub-clinical exposure, there is no evidence that Fetcroja has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were diarrhoea (8.2%), vomiting (3.6%), nausea (3.3%) and cough (2%).

Tabulated list of adverse reactions

The following adverse reactions have been reported with cefiderocol during clinical studies (Table 3). 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 $< 1/1000$); 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 3 Tabulated list of adverse reactions

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known
<i>Infections and infestations</i>	Candidiasis including oral candidiasis, vulvovaginal candidiasis, candiduria and candida infection, <i>Clostridioides difficile</i> colitis including pseudomembranous colitis and <i>Clostridioides difficile</i> infection		
Blood and lymphatic system disorders			Neutropenia
<i>Immune System Disorders</i>		Hypersensitivity including skin reactions and Pruritus	
<i>Respiratory, thoracic and mediastinal disorders</i>	Cough		
<i>Gastrointestinal disorders</i>	Diarrhoea, Nausea, Vomiting		
<i>Skin and subcutaneous tissue disorders</i>	Rash including rash macular, rash maculopapular, rash erythematous and drug eruption		
<i>General disorders and administration site conditions</i>	Infusion site reaction including infusion site pain, injection site pain, infusion site erythema and injection site phlebitis		
<i>Investigations</i>	Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Aspartate aminotransferase increased, Hepatic function abnormal including liver function test increased, hepatic enzyme increased, transaminases increased and liver function test abnormal, Blood creatinine increased	Blood urea increased	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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.

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 and death.

Resistance

Mechanisms of bacterial resistance that may lead to resistance to cefiderocol include mutant or acquired 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 effect of cefiderocol against normally susceptible species 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.

Antibacterial activity in combination with other antibacterial agents

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

Susceptibility testing breakpoints

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

Organisms	Minimum inhibitory concentrations (mg/L)	
	Susceptible	Resistant
Enterobacterales	≤2	>2
<i>Pseudomonas aeruginosa</i>	≤2	>2

Pharmacokinetic/pharmacodynamic relationship

The time that unbound plasma concentrations of cefiderocol exceeds the minimum inhibitory concentration ($\%fT_{>MIC}$) against the infecting organism has been shown to best correlate with efficacy.

Antibacterial activity against specific pathogens

In-vitro studies suggest that the following pathogens would be susceptible to cefiderocol in the absence of acquired mechanisms of resistance:

Aerobic Gram-negative organisms

Achromobacter spp.
Acinetobacter baumannii complex
Burkholderia cepacia complex
Citrobacter freundii complex
Citrobacter koseri
Escherichia coli
Enterobacter cloacae complex
Klebsiella (Enterobacter) aerogenes
Klebsiella pneumoniae
Klebsiella oxytoca
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Serratia spp.
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia

In vitro studies indicate that the following species are not susceptible to cefiderocol:

Aerobic Gram-positive organisms

Anaerobic organisms

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fetcroja in one or more subsets of the paediatric population in the treatment of infections due to aerobic Gram-negative bacteria (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After multiple dose administration of cefiderocol, there is no accumulation of cefiderocol administered every 8 hours in healthy adult subjects with normal renal function.

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.

Biotransformation

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. The most predominant metabolite, pyrrolidine chlorobenzamide (PCBA, which is a degradation product of cefiderocol), accounted for 4.7% of the plasma AUC for total radioactivity, while other more minor metabolites each accounted for < 2% of the plasma AUC for total radioactivity.

Interaction with other medicinal products.

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

Elimination

The terminal elimination half-life in healthy adult subjects was 2 to 3 hours. The geometric mean (%CV) of clearance of cefiderocol in healthy subjects is estimated to be 5.18 (17.2%) L/hr. Cefiderocol is primarily eliminated by the kidneys. 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.

Linearity/non-linearity

Cefiderocol exhibits linear pharmacokinetics within the dose range of 100 mg to 4000 mg.

Special populations

In a population pharmacokinetic analysis, no clinically relevant effect on the pharmacokinetics of cefiderocol was observed with respect to age, gender or race.

Paediatric population

Pharmacokinetic studies have not been performed with cefiderocol in infants and children under 18 years of age (see section 4.2).

Renal impairment

The pharmacokinetics of cefiderocol after administration of a single 1 g dose was assessed in subjects with mild renal impairment (n=8, estimated glomerular filtration rate [eGFR] of 60 to < 90 mL/min/1.73 m²), moderate renal impairment (n=7, eGFR 30 to < 60 mL/min/1.73 m²), severe renal impairment (n=6, eGFR less than 30 mL/min/1.73 m²), end-stage renal disease (ESRD) requiring haemodialysis (n=8), and healthy subjects with normal renal function (n=8, estimated creatinine clearance of at least 90 mL/min). The geometric mean ratios (GMR; mild, moderate, severe or ESRD without haemodialysis/normal renal function) and 90% confidence intervals (CI) for the AUC of cefiderocol were 1.0 (0.8, 1.3), 1.5 (1.2, 1.9), 2.5 (2.0, 3.3) and 4.1 (3.3, 5.2), respectively. Approximately 60% of Fetroja was removed by a 3- to 4-hour haemodialysis session.

The recommended dose adjustments in subjects with varying degrees of renal impairment are expected to provide comparable exposures to subjects with normal renal function or mild renal impairment (see section 4.2).

Patients with augmented renal clearance

Simulations using the population PK model demonstrated that the recommended dose adjustment for ARC provide exposures, including %T>MIC, of Fetroja comparable to those in patients with normal renal function.

Hepatic impairment

Hepatic impairment is not expected to alter the elimination of Fetcroja as hepatic metabolism/excretion represent a minor pathway of elimination of Fetcroja.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, or genotoxicity. Carcinogenicity studies with cefiderocol have not been conducted.

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). There was no evidence of *in vivo* genotoxicity (rat micronucleus assay and comet assay in rats).

Cefiderocol had no impairment of fertility and early embryonic development in rats treated with cefiderocol intravenously up to 1000 mg/kg/day corresponding to a margin to clinical exposure of 0.8. There was no evidence of teratogenicity or embryotoxicity in rats or mice that received 1000 mg/kg/day or 2000 mg/kg/day respectively corresponding to margins to clinical exposure of 0.9 and 1.3

Cefiderocol had no adverse effects on growth and development, including neurobehavioural function in juvenile rats that received 1000 mg/kg/day subcutaneously during postnatal day (PND)7 to PND27, or 600 mg/kg/day intravenously from PND28 to PND48.

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 6.6.

6.3 Shelf life

Powder

3 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 (see section 4.2). 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 6.6.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 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.

6.5 Nature and contents of container

14 mL vial (Type I clear glass vial), chlorobutyl elastomeric stopper, and aluminum 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 and other handling

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 cefiderocol doses

Cefiderocol 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	11.2 mL (entire contents) from both vials	22.4 mL
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.

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

7. MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1434/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 april 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ACS Dobfar S.P.A.
Nucleo Industriale S. Atto
Localita S. Nicolo a Tordino
64100
Teramo
ITALY

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fetroja 1 g powder for concentrate for solution for infusion
cefiderocol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sucrose, sodium chloride and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use
Dilute before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Kingsfordweg 151
1043GR Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1434/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fetroja 1 g powder for concentrate
cefiderocol
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 g

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Fetroja 1 g powder for concentrate for solution for infusion cefiderocol

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects, you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fetroja is and what it is used for
2. What you need to know before you are given Fetroja
3. How Fetroja is used
4. Possible side effects
5. How to store Fetroja
6. Contents of the pack and other information

1. What Fetroja is and what it is used for

Fetroja contains the active substance cefiderocol. It is an antibiotic medicine that belongs to a group of antibiotics called cephalosporins. Antibiotics help to fight bacteria that cause infections.

Fetroja is used in adults to treat infections caused by certain types of bacteria when other antibiotics cannot be used.

2. What you need to know before you are given Fetroja

Do not use Fetroja

- if you are **allergic to cefiderocol** or any of the other ingredients of this medicine (listed in section 6);
 - if you are **allergic to other antibiotics** known as cephalosporins;
 - if you have had a **severe allergic reaction to certain antibiotics**, such as penicillins or carbapenems. This can include severe skin peeling, swelling of the hands, face, feet, lips, tongue or throat; or difficulty swallowing or breathing.
- ➔ **Tell your doctor** if any of these apply to you.

Warnings and precautions

Talk to your doctor or nurse before you are given Fetroja:

- if you have ever had any **allergic reaction to other antibiotics**. See also section above, “Do not use Fetroja”;
- if you have **kidney problems**. Your doctor will adjust your dose to ensure you don’t get too much or too little medicine;
- if you suffer from **diarrhoea** during your treatment;
- if you are on a **low sodium diet**;
- if you have ever had **seizures**.

➔ **Talk to your doctor or nurse** before you are given Fetroja.

New Infection

Although Fetroja can fight certain bacteria, there is a possibility that you may get a different infection caused by another organism during or after your treatment. Your doctor will monitor you closely for any new infections and give you another treatment if necessary.

Blood/laboratory Tests

Tell your doctor that you are taking Fetroja if you are going to have any blood/laboratory tests. This is because you may get an abnormal result. With something called a “Coombs test” this looks for the presence of antibodies that can destroy red blood cells or may be affected by the response of your immune system to Fetroja. Fetroja may also result in false-positive results in urine dipstick tests (urine protein or diabetes markers).

Children and adolescents

Fetroja should not be given to children and adolescents under the age of 18. This is because it is not known if the medicine is safe to use in these age groups.

Other medicines and Fetroja

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

Fetroja does not affect your ability to drive or operate machinery.

Fetroja contains sodium

This medicine contains 7.64 mmol (176 mg) of sodium per vial. The total daily dose is 2.1 g, just greater than the WHO recommend daily maximum of 2 g sodium for an adult. Talk to your doctor before you are given Fetroja if you are on a low sodium diet.

3. How Fetroja is used

Your doctor or nurse will give you this medicine as an infusion (a drip) into your vein over 3 hours, three times a day. The usual recommended dose is 2 g.

The number of days you will be given Fetroja treatment depends on the type of infection you have and how well your infection is clearing.

If you get any pain where the Fetroja infusion goes into your vein, tell your doctor or nurse.

People with kidney problems

If you have kidney problems, talk to your doctor before you are given Fetroja. The doctor will adjust your dose of Fetroja.

If you are given more Fetroja than you should

Fetroja will be given to you by a doctor or nurse, so it is unlikely you will be given the wrong dose. Tell your doctor or nurse straight away if you think you have been given more Fetroja than you should have.

If you miss a dose of Fetroja

If you think you have not been given a dose of Fetroja, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- **Severe allergic reaction** – signs include sudden swelling of your lips, face, throat or tongue; a severe rash or other severe skin reactions; difficulty swallowing or breathing. This reaction may be life-threatening.
 - **Diarrhoea** that gets worse or does not go away, or stools that contain blood or mucus. This may happen during treatment, or after it has been stopped. If this happens, do not take medicines that stop or slow bowel movement.
- ➔ **Tell your doctor** straight away if you notice any of the serious side effects above.

Other side effects

Tell your doctor or nurse if you notice any of the following side effects.

Common

(may affect up to 1 in 10 people)

- Feeling sick (nausea) or being sick (vomiting)
- Swelling, redness and/or pain around the needle where the medicine is given into a vein
- Yeast infections e.g. thrush
- Increase in levels of liver enzymes, shown in blood tests
- Cough
- Rash, with small raised bumps
- Severe gut infection known as *Clostridioides difficile* colitis. Symptoms include watery diarrhoea, abdominal pain, fever, etc.
- Increased blood creatinine values

Uncommon

(may affect up to 1 in 100 people)

- Increased blood urea values
- Allergy to Fetroja

Not known

(frequency cannot be estimated from the available data)

- Reduced count of specific white blood cells (neutrophil granulocytes)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Fetroja

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Store unopened vials in a refrigerator (2°C - 8°C).

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fetroja contains

- The active substance is cefiderocol sulfate tosylate, equivalent to 1 g cefiderocol.
- The other excipients are sucrose, sodium chloride and sodium hydroxide.

What Fetroja looks like and contents of the pack

Fetroja is a white to off-white powder for concentrate for solution for infusion in a vial. It is available in packs containing 10 vials.

Marketing Authorisation Holder

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Kingsfordweg 151
1043GR Amsterdam
Netherlands

Manufacturer

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(loc. S. Nicolo' a Tordino)
64100 Teramo (TE)

Shionogi B.V.
Kingsfordweg 151
1043GR Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

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 the table below. 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.

Preparation of cefiderocol doses

Cefiderocol 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	11.2 mL (entire contents) from both vials	22.4 mL
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.

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for cefiderocol, the scientific conclusions of CHMP are as follows:

In view of available data on “blood urea increased”, “blood creatinine increased” and “neutropenia” from clinical trials and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between cefiderocol and “blood urea increased”, “blood creatinine increased” and “neutropenia” is at least a reasonable possibility. The PRAC concluded that the product information of products containing cefiderocol should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for cefiderocol the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing cefiderocol is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.