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**

Fetcroja 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

Fetcroja 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 Fetcroja 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>
<thead>
<tr>
<th>Renal function</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function (CrCL ≥90 to &lt; 120 mL/min)</td>
<td>2 g</td>
<td>Every 8 hours</td>
<td>Duration in accordance with the site of infection³</td>
</tr>
<tr>
<td>Augmented renal clearance (CrCL ≥ 120 mL/min)</td>
<td>2 g</td>
<td>Every 6 hours</td>
<td>Duration in accordance with the site of infection³</td>
</tr>
</tbody>
</table>

³To be used in combination with antibacterial agents active against anaerobic pathogens and/or Gram-positive
Special populations

Renal impairment

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild renal impairment</td>
<td>2 g</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>(CrCL ≥60 to &lt; 90 mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate renal impairment</td>
<td>1.5 g</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>(CrCL ≥30 to &lt; 60 mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>1 g</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>(CrCL ≥15 to &lt; 30 mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>0.75 g</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>(CrCL &lt; 15 mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient with intermittent haemodialysis</td>
<td>0.75 g</td>
<td>Every 12 hours</td>
</tr>
</tbody>
</table>

1As calculated using the Cockcroft-Gault formula.
2As ceferodol 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 Fetcroja in children below 18 years of age has not yet been established. No data are available.

Method of administration
Intravenous use.
Fetcroja 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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>
<thead>
<tr>
<th>System organ class</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Candidiasis including oral candidiasis, vulvovaginal candidiasis, candiduria and candida infection, <em>Clostridioides difficile</em> colitis including pseudomembranous colitis and <em>Clostridioides difficile</em> infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea, Nausea, Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash including rash macular, rash maculopapular, rash erythematous and drug eruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Infusion site reaction including infusion site pain, injection site pain, infusion site erythema and injection site phlebitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>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</td>
<td></td>
<td>Blood urea increased</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Minimum inhibitory concentrations (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Enterobacterales</td>
<td>≤2</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤2</td>
</tr>
</tbody>
</table>
Pharmacokinetic/pharmacodynamic relationship

The time that unbound plasma concentrations of cefiderocol exceeds the minimum inhibitory concentration (\(\%T_{\text{MIC}}\)) 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.
- Actinetobacter baumannii complex
- Burkholderia cepacia complex
- Citrobacter freundii complex
- Citrobacter koseri
- Escherichia coli
- Enterobacter cloacae complex
- Klebsiella (Enterobacter) aerogenes
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Morganella morgani
- 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 Fetcroja 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 Fetcroja 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

<table>
<thead>
<tr>
<th>Cefiderocol dose</th>
<th>Number of 1 g cefiderocol vials to be reconstituted</th>
<th>Volume to withdraw from reconstituted vial(s)</th>
<th>Total volume of cefiderocol solution required for further dilution in at least 100 mL of 0.9% sodium chloride injection or 5% dextrose injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
<td>2 vials</td>
<td>11.2 mL (entire contents) from both vials</td>
<td>22.4 mL</td>
</tr>
<tr>
<td>1.5 g</td>
<td>2 vials</td>
<td>11.2 mL (entire contents) from first vial AND 5.6 mL from second vial</td>
<td>16.8 mL</td>
</tr>
<tr>
<td>1 g</td>
<td>1 vial</td>
<td>11.2 mL (entire contents)</td>
<td>11.2 mL</td>
</tr>
<tr>
<td>0.75 g</td>
<td>1 vial</td>
<td>8.4 mL</td>
<td>8.4 mL</td>
</tr>
</tbody>
</table>

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 AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/20/1434/001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

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

Feteroja 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**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feteroja 1 g powder for concentrate</td>
</tr>
<tr>
<td>cefiderocol</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
B. PACKAGE LEAFLET
Package leaflet: Information for the user

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

1. What Fetcroja is and what it is used for

Fetcroja 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.

Fetcroja 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 Fetcroja

Do not use Fetcroja
- 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 carabapenems. 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 Fetcroja:
- if you have ever had any allergic reaction to other antibiotics. See also section above, “Do not use Fetcroja”;
- 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 Fetcroja.

New Infection
Although Fetcroja 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 Fetcroja 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 Fetcroja. Fetcroja may also result in false-positive results in urine dipstick tests (urine protein or diabetes markers).

Children and adolescents
Fetcroja 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 Fetcroja
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
Fetcroja does not affect your ability to drive or operate machinery.

Fetcroja 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 Fetcroja if you are on a low sodium diet.

3. How Fetcroja 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 Fetcroja treatment depends on the type of infection you have and how well your infection is clearing.

If you get any pain where the Fetcroja 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 Fetcroja. The doctor will adjust your dose of Fetcroja.

If you are given more Fetcroja than you should
Fetcroja 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 Fetcroja than you should have.

If you miss a dose of Fetcroja
If you think you have not been given a dose of Fetcroja, 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 Fetcroja

**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 Fetcroja

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

What Fetcroja looks like and contents of the pack
Fetcroja 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
Shionogi B.V.
Kingsfordweg 151
1043GR Amsterdam
Netherlands

Manufacturer
ACS DOBFAR S.P.A
Nucleo Industriale S. Atto
(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:

AT, BE, BG, CY, CZ, DK, EE, EL, FI, HR, HU, IE, IS, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK
Shionogi B.V. Tel/Tel./ Tel./ Tél/ Tél/ Puh/
Sími/ Tηλ./
+31 (0) 20 703 8327
contact@shionogi.eu

España
Shionogi SLU
Tel: + 34 911 239 258
contacta@shionogi.eu

UK (NI)
Shionogi B.V.
Tel: + 44 (0) 2891248945
contact@shionogi.eu

This leaflet was last revised in.
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

<table>
<thead>
<tr>
<th>Cefiderocol dose</th>
<th>Number of 1 g cefiderocol vials to be reconstituted</th>
<th>Volume to withdraw from reconstituted vial(s)</th>
<th>Total volume of cefiderocol solution required for further dilution in at least 100 mL of 0.9% sodium chloride injection or 5% dextrose injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
<td>2 vials</td>
<td>11.2 mL (entire contents) from both vials</td>
<td>22.4 mL</td>
</tr>
<tr>
<td>1.5 g</td>
<td>2 vials</td>
<td>11.2 mL (entire contents) from first vial AND 5.6 mL from second vial</td>
<td>16.8 mL</td>
</tr>
<tr>
<td>1 g</td>
<td>1 vial</td>
<td>11.2 mL (entire contents)</td>
<td>11.2 mL</td>
</tr>
<tr>
<td>0.75 g</td>
<td>1 vial</td>
<td>8.4 mL</td>
<td>8.4 mL</td>
</tr>
</tbody>
</table>

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.