Updated September 2020

Hospital Pharmacy
Product Information Form

This resource is intended for a payer, formulary committee, or other similar entities with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement.

Fetroja® (cefiderocol) for injection

INDICATIONS

Fetroja® (cefiderocol) is indicated in patients 18 years of age or older for the treatment of 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.

Fetroja is indicated in patients 18 years of age or older for the treatment of 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*.

USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Fetroja and other antibacterial drugs, Fetroja should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

1. GENERIC NAME[1]:

cefiderocol

2. THERAPEUTIC NAME[1]:

Fetroja

3. THERAPEUTIC CLASS[1]:

Fetroja is a cephalosporin antibacterial drug.

4. SOURCE OF SUPPLY[1]:

Shionogi & Co., Ltd.
Osaka 541-0045
Japan

5. NEW DRUG APPLICATION (NDA) NUMBER AND DATE OF FDA APPROVAL[2,3]:

NDA 209445, approved November 14, 2019

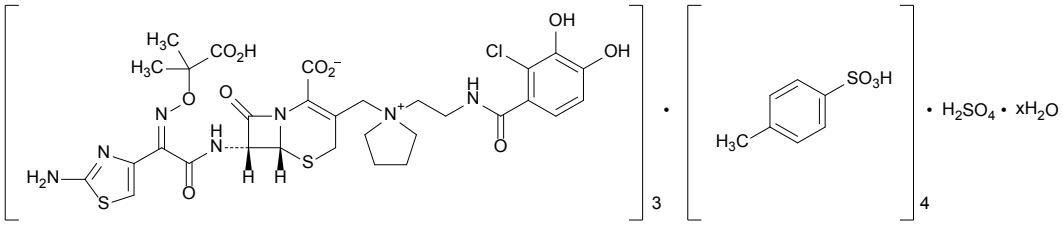
6. PHYSICAL PROPERTIES[1]:

Fetroja 1 gram for injection is supplied as a white to off-white, sterile, lyophilized powder for reconstitution in single-dose, clear glass vials; each vial contains 1 gram of cefiderocol.

7. CHEMICAL PROPERTIES[1]:

Fetroja is a cephalosporin antibacterial drug product consisting of cefiderocol sulfate tosylate for intravenous infusion. Cefiderocol functions as a siderophore.

The chemical name of cefiderocol sulfate tosylate is Tris[(6*R*,7*R*)-7-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl] pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate] tetrakis (4-methylbenzenesulfonate) monosulfate hydrate, and the molecular weight is 3043.50 (anhydrous). The molecular formula is $3C_{30}H_{34}C1N_7O_{10}S_2 \bullet 4C_7H_8O_3S \bullet H_2SO_4 \bullet xH_2O$.



Fetroja for injection is a white to off-white, sterile, lyophilized powder formulated with 1 gram of cefiderocol (equivalent to 1.6 grams of cefiderocol sulfate tosylate), sucrose (900 mg), sodium chloride (216 mg), and sodium hydroxide to adjust pH. The sodium content is approximately 176 mg/vial. The pH of the reconstituted solution of 1 gram cefiderocol (1 vial) dissolved in 10 mL water is 5.2 to 5.8.

8. PHARMACOLOGIC CLASSIFICATION[1]:

Mechanism of Action

Fetroja is an antibacterial drug.

Pharmacodynamics

The percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the minimum inhibitory concentration (MIC) against the infecting organism best correlates with antibacterial activity in neutropenic murine thigh and lung infection models with *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. Compared to a 1-hour infusion, a 3-hour infusion increased the percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the MIC. The in vivo animal pneumonia studies showed that the antibacterial activity of cefiderocol was greater at the human equivalent dosing regimen of 3-hour infusion compared to that of 1-hour infusion.

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

Cardiac Electrophysiology

At doses 1 and 2 times the maximum recommended dosage, Fetroja does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics

Cefiderocol exposures (C_{max} and daily AUC) in cUTI patients, HABP/VABP patients and healthy volunteers are summarized in Table 1. Cefiderocol C_{max} and AUC increased proportionally with dose.

Table 1 Cefiderocol Exposures Mean (±SD) in Patients and Healthy Volunteers with CLcr 60 mL/min or Greater

PK parameters	cUTI patients* (N=21)	HABP/VABP patients* (N=146)	Healthy volunteers† (N=43)
C_{max} (mg/L)	115 (±57)	111 (±56)	91.4 (±17.9)

*After multiple (every 8 hours) Fetroja 2-gram doses infused over 3 hours or adjusted based on renal function
†After a single Fetroja 2-gram dose was infused over 3 hours

Distribution

The geometric mean (±SD) cefiderocol volume of distribution was 18.0 (±3.36) L. Plasma protein binding, primarily to albumin, of cefiderocol is 40% to 60%.

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

Elimination

Cefiderocol terminal elimination half-life is 2 to 3 hours. The geometric mean (±SD) cefiderocol clearance is estimated to be 5.18 (±0.89) L/hr.

Metabolism

Cefiderocol is minimally metabolized [less than 10% of a single radiolabeled cefiderocol dose of 1 gram (0.5 times the approved recommended dosage) infused over 1 hour].

Excretion

Cefiderocol is primarily excreted by the kidneys. After a single radiolabeled cefiderocol 1-gram (0.5 times the approved recommended dosage) dose infused over 1 hour, 98.6% of the total radioactivity was excreted in urine (90.6% unchanged) and 2.8% in feces.

Specific Populations

No clinically significant differences in the pharmacokinetics of cefiderocol were observed based on age (18 to 93 years of age), sex, or race. The effect of hepatic impairment on the pharmacokinetics of cefiderocol was not evaluated.

Patients With Renal Impairment

Approximately 60% of cefiderocol was removed by a 3- to 4-hour hemodialysis (HD) session.

Cefiderocol AUC fold changes in subjects with renal impairment compared to subjects with CLcr 90 to 119 mL/min are summarized in Table 2.

Table 2 Effect of Renal Impairment on the AUC of Cefiderocol‡

CLcr (mL/min)	Cefiderocol AUC geometric mean ratios (90% CI)§
60 to 89 (N=6)	1.37 (1.15, 1.62)
30 to 59 (N=7)	2.35 (2.00, 2.77)
15 to 29 (N=4)	3.21 (2.64, 3.91)
<15 (N=6)	4.69 (3.95, 5.56)

‡After a single Fetroja 1-gram dose (0.5 times the approved recommended dosage)
§ Compared to AUC in subjects with CLcr 90 to 119 mL/min (N=12)

AUC=area under the concentration-time curve; $AUC_{0\text{-}24\ hrs}$=area under the concentration time curve from 0 to 24 hours; CI=confidence interval; CLcr=creatinine clearance; C_{max}=maximum plasma concentration; cUTI=complicated urinary tract infection; HABP=hospital-acquired bacterial pneumonia; SD=standard deviation; VABP=ventilator-associated bacterial pneumonia.

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

Patients Receiving CRRT

In an in vitro study, effluent flow rate was the major determinant of cefiderocol clearance by CRRT. Variables examined included effluent flow rate, CRRT mode (CVVH or CVVHD), filter type and point of dilution (pre- or post-filter dilution). The effluent flow rate-based dosing recommendations in Table 4 are predicted to provide cefiderocol exposures similar to those achieved with a dose of 2 grams given every 8 hours in patients not receiving CRRT.

Patients With CLcr 120 mL/min or Greater

Increased cefiderocol clearance has been observed in patients with CLcr 120 mL/min or greater. A Fetroja 2-gram dose every 6 hours infused over 3 hours provided cefiderocol exposures comparable to those in patients with CLcr 90 to 119 mL/min.

Drug Interaction Studies

Clinical Studies

No clinically significant differences in the pharmacokinetics of furosemide (an organic anion transporter [OAT]1 and OAT3 substrate), metformin (an organic cation transporter [OCT]1, OCT2, and multidrug and toxin extrusion [MATE]2-K substrate), and rosuvastatin (an organic anion transporting polypeptide [OATP]1B3 substrate) were observed when coadministered with cefiderocol.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Cytochrome P450 (CYP) Enzymes: Cefiderocol is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Cefiderocol is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Cefiderocol is not an inhibitor of OATP1B1, MATE1, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or bile salt export pump transporters. Cefiderocol is not a substrate of OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP.

Microbiology

Mechanism of Action

Fetroja is a cephalosporin antibacterial with activity against Gram-negative aerobic bacteria. Cefiderocol functions as a siderophore and binds to extracellular free (ferric) iron. In addition to passive diffusion via porin channels, cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using the bacterial siderophore iron uptake mechanism. Cefiderocol exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins (PBPs).

Cefiderocol has no clinically relevant in vitro activity against most Gram-positive bacteria and anaerobic bacteria.

Resistance

In vitro, MIC increases that may result in resistance to cefiderocol in Gram-negative bacteria have been associated with a combination of multiple beta-lactamases, modifications of PBPs, and mutations of transcriptional regulators that impact siderophore expression.

Cefiderocol does not cause induction of AmpC beta-lactamase in *P aeruginosa* and *Enterobacter cloacae*. The frequency of resistance development in Gram-negative bacteria including carbapenemase producers exposed to cefiderocol at 10x MIC ranged from 10^{-6} to $<10^{-8}$.

Cross-resistance with other classes of antibacterial drugs has not been identified; therefore, isolates resistant to other antibacterial drugs may be susceptible to cefiderocol.

Cefiderocol has shown in vitro activity against isolates of *S maltophilia* and a subset of isolates of Enterobacterales and *P aeruginosa* that are resistant to meropenem, ciprofloxacin, amikacin, cefepime, ceftazidime-avibactam, and ceftolozane/tazobactam. Cefiderocol has shown in vitro activity against subset of isolates of *A baumannii* complex that are resistant to meropenem, ciprofloxacin, and amikacin. Cefiderocol is active against some colistin-resistant *E coli* isolates containing *mcr-1*.

Cefiderocol demonstrated in vitro activity against a subgroup of Enterobacterales genetically confirmed to contain the following: ESBLs (TEM, SHV, CTX-M, oxacillinase [OXA]), AmpC, AmpC-type ESBL (CMY), serine-carbapenemases (such as KPC, OXA-48), and metallo-carbapenemases (such as NDM and VIM). Cefiderocol demonstrated in vitro activity against a subgroup of *P aeruginosa* genetically confirmed to contain VIM, IMP, GES, AmpC, and a subgroup of *A baumannii* containing OXA-23, OXA-24/40, OXA-51, OXA-58, and AmpC. Cefiderocol is active in vitro against a subgroup of *S maltophilia* containing metallo-carbapenemase (L1) and serine beta-lactamases (L2).

Cefiderocol maintained in vitro activity against *K pneumoniae* in the presence of porin channel deletions (OmpK35/36), and against *P aeruginosa* in the presence of porin channel deletions (OprD) and efflux pump up-regulation (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY).

In vitro, the addition of the beta-lactamase inhibitors (such as avibactam, clavulanic acid, and dipicolinic acid) results in the lowering of MICs of some clinical isolates with relatively high MICs (range 2 to 256 mcg/mL) to cefiderocol.

CRRT=continuous renal replacement therapy; CVVH=continuous venovenous hemofiltration; CVVHD=continuous venovenous hemodialysis and continuous venovenous hemodiafiltration; ESBL=extended-spectrum beta-lactamase.

Interaction With Other Antimicrobials
In vitro studies showed no antagonism between cefiderocol and amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline, or vancomycin against strains of Enterobacterales, *P aeruginosa*, and *A baumannii*.

Activity Against Bacteria in Animal Infection Models
In a neutropenic murine thigh infection model using a humanized dose (2 grams every 8 hours), cefiderocol demonstrated 1$\log_{10}$ reduction in bacterial burden against most *E coli*, *K pneumoniae*, *A baumannii, S maltophilia*, and *P aeruginosa* including some carbapenemase-producing (KPC, OXA-23, OXA-24/40, OXA-58) isolates with MICs of ≤4 mcg/mL to cefiderocol.

In an immunocompetent rat pneumonia model, reduction in bacterial counts in the lungs of animals infected with *K pneumoniae* with MICs ≤8 mcg/mL, *A baumannii* with MICs ≤2 mcg/mL, and *P aeruginosa* with MICs ≤1 mcg/mL, including carbapenemase (KPC, NDM and IMP) producing isolates was observed using humanized cefiderocol drug exposure.

In an immunocompetent murine urinary tract infection model, cefiderocol reduced bacterial counts in the kidneys of mice infected with *E coli*, *K pneumoniae*, and *P aeruginosa* isolates with MICs ≤1 mcg/mL. In an immunocompromised murine systemic infection model, cefiderocol increased survival in mice infected with *E cloacae*, *S maltophilia*, and *Burkholderia cepacia* isolates with MICs ≤0.5 mcg/mL compared to untreated mice. In an immunocompetent murine systemic infection model, cefiderocol increased survival in mice infected with *Serratia marcescens* and *P aeruginosa* isolates with MICs ≤1 mcg/mL compared to untreated mice.

The clinical significance of the above findings in animal infection models is not known.

Antimicrobial Activity
Fetroja has been shown to be active against the following bacteria, both in vitro and in clinical infections.

Complicated Urinary Tract Infections, Including Pyelonephritis

Gram-negative bacteria

Escherichia coli
Enterobacter cloacae complex
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

Gram-negative bacteria

Acinetobacter baumannii complex
Escherichia coli
Enterobacter cloacae complex
Klebsiella pneumoniae
Pseudomonas aeruginosa
Serratia marcescens

The following in vitro data are available, but their clinical significance is not known. At least 90% of the following bacteria exhibit an in vitro MIC less than or equal to the susceptible breakpoint for Fetroja against isolates of similar genus or organism group. However, the efficacy of Fetroja in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Achromobacter spp
Burkholderia cepacia complex
Citrobacter freundii complex
Citrobacter koseri
Klebsiella aerogenes
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Stenotrophomonas maltophilia

Susceptibility Testing
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see https://www.fda.gov/STIC.

9. DOSAGE AND ADMINISTRATION[1]:

Recommended Dosage

The recommended dosage of Fetroja is 2 grams administered every 8 hours by intravenous (IV) infusion over 3 hours in adults with a CLcr of 60 to 119 mL/min.

Dosage adjustment of Fetroja is recommended for patients with CLcr less than 60 mL/min, including patients receiving intermittent HD or CRRT, and for patients with CLcr 120 mL/min or greater. The recommended duration of treatment with Fetroja is 7 to 14 days. The duration of therapy should be guided by the patient's clinical status.

Dosage Adjustments in Patients With CLcr Less Than 60 mL/min (Including Patients Undergoing Intermittent HD or CRRT), and CLcr 120 mL/min or Greater

Dosage Adjustments in Patients With CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Dosage adjustment of Fetroja is recommended in patients with CLcr less than 60 mL/min (Table 3). For patients undergoing intermittent HD, start the dosing of Fetroja immediately after the completion of HD. For patients with fluctuating renal function, monitor CLcr and adjust dosage accordingly.

Table 3 Recommended Dosage of Fetroja for Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Estimated CLcr*	Dose	Frequency	Infusion time
CLcr 30 to 59 mL/min	1.5 grams	Every 8 hours	3 hours
CLcr 15 to 29 mL/min	1 gram	Every 8 hours	3 hours
CLcr less than 15 mL/min, with or without intermittent HD†	0.75 gram	Every 12 hours	3 hours

HD=hemodialysis.
*CLcr=creatinine clearance estimated by Cockcroft-Gault equation
†Cefiderocol is removed by HD; administer Fetroja immediately after HD for patients receiving intermittent HD.

Dosage Adjustments in Patients Receiving CRRT

For patients receiving CRRT, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF), the dosage of Fetroja should be based on the effluent flow rate in CRRT (see Table 4). These recommendations are intended to provide initial dosing in patients receiving CRRT. Dosing regimens may need to be tailored based on residual renal function and patient's clinical status.

Table 4 Recommended Dosage of Fetroja for Patients Receiving CRRT

Effluent flow rate‡	2 L/hr or less	2.1 to 3 L/hr	3.1 to 4 L/hr	4.1 L/hr or greater
Recommended Dosage of Fetroja	1.5 grams every 12 hours	2 grams every 12 hours	1.5 grams every 8 hours	2 grams every 8 hours

‡Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF

Dosage Adjustments in Patients With CLcr 120 mL/min or Greater

For patients with CLcr greater than or equal to 120 mL/min, Fetroja 2 grams administered every 6 hours by IV infusion over 3 hours is recommended.

Overdosage

There is no information on clinical signs and symptoms associated with an overdose of Fetroja. Patients who receive doses greater than the recommended dose regimen and have unexpected adverse reactions possibly associated with Fetroja should be carefully observed and given supportive treatment, and discontinuation or interruption of treatment should be considered.

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

Preparation of Fetroja Solution for Administration

Fetroja is supplied as a sterile, lyophilized powder that must be reconstituted and subsequently diluted using aseptic technique prior to intravenous infusion.

Preparation of Doses

Reconstitute the powder for injection in the Fetroja vial with 10 mL of either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP and gently shake to dissolve. Allow the vial(s) to stand until the foaming generated on the surface has disappeared (typically within 2 minutes). The final volume of the reconstituted solution will be approximately 11.2 mL. The reconstituted solution is for intravenous infusion only after dilution in an appropriate infusion solution.

To prepare the required doses, withdraw the appropriate volume of reconstituted solution from the vial according to Table 5 on the following page. Add the withdrawn volume to a 100 mL infusion bag containing 0.9% sodium chloride injection, USP or 5% dextrose injection, USP.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Fetroja infusions are clear, colorless solutions. Discard any unused Fetroja solution in the vial (see Table 5).

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

Table 5 Preparation of Fetroja Doses

Fetroja dose	Number of 1-gram Fetroja vials to be reconstituted	Volume to withdraw from reconstituted vial(s)	Total volume of Fetroja reconstituted solution for further dilution into a 100 mL infusion bag
2 grams	2 vials	11.2 mL (entire contents) of each vial	22.4 mL
1.5 grams	2 vials	11.2 mL (entire contents) of first vial AND 5.6 mL from second vial	16.8 mL
1 gram	1 vial	11.2 mL (entire contents)	11.2 mL
0.75 gram	1 vial	8.4 mL	8.4 mL

Drug Compatibility

Fetroja solution for administration is compatible with:

- 0.9% sodium chloride injection, USP
- 5% dextrose injection, USP

The compatibility of Fetroja solution for administration with solutions containing other drugs or other diluents has not been established.

Storage of Reconstituted Solutions

Reconstituted Fetroja

Upon reconstitution with the appropriate diluent, the reconstituted Fetroja solution in the vial should be immediately transferred and diluted into the infusion bag. Reconstituted Fetroja can be stored for up to 1 hour at room temperature in the vial. Discard any unused reconstituted solution.

Diluted Fetroja Infusion Solution

The diluted Fetroja infusion solution in the infusion bag is stable for up to 6 hours at room temperature.

The diluted Fetroja infusion solution in the infusion bag may also be refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light; and then the infusion should be completed within 6 hours at room temperature.

Storage and Handling

Fetroja vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Store in the carton until time of use. Store reconstituted solutions of Fetroja at room temperature.

How Supplied

Fetroja 1 gram (cefiderocol) for injection is supplied as a white to off-white sterile lyophilized powder for reconstitution in single-dose, clear glass vials (NDC 59630-266-01) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum seal with flip-off cap. Each vial is supplied in cartons containing 10 single-dose vials.

- NDC 59630-266-10 Fetroja (cefiderocol) 1 gram/vial, 10 vials/carton

10. ADVERSE REACTIONS[1]:

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis

Fetroja was evaluated in an active-controlled, randomized clinical trial in patients with cUTI, including pyelonephritis (Trial 1). In this trial, 300 patients received Fetroja 2 grams every 8 hours infused over 1 hour (or a renally-adjusted dose), and 148 patients were treated with imipenem/cilastatin 1 gram/1 gram every 8 hours infused over 1 hour (or a renally-adjusted dose). The median age of treated patients across treatment arms was 65 years (range 18 to 93 years), with approximately 53% of patients aged greater than or equal to 65. Approximately 96% of patients were White, most were from Europe, and 55% were female. Patients across treatment arms received treatment for a median duration of 9 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 1, a total of 14/300 (4.7%) cUTI patients treated with Fetroja and 12/148 (8.1%) of cUTI patients treated with imipenem/cilastatin experienced serious adverse reactions. One death (0.3%) occurred in 300 patients treated with Fetroja as compared to none treated with imipenem/cilastatin. Discontinuation of treatment due to any adverse reaction occurred in 5/300 (1.7%) of patients treated with Fetroja and 3/148 (2.0%) of patients treated with imipenem/cilastatin. Specific adverse reactions leading to treatment discontinuation in patients who received Fetroja included diarrhea (0.3%), drug hypersensitivity (0.3%), and increased hepatic enzymes (0.3%).

Common Adverse Reactions

Table 6 lists the most common selected adverse reactions occurring in ≥2% of cUTI patients receiving Fetroja in Trial 1.

Table 6 Selected Adverse Reactions Occurring in ≥2% Of cUTI Patients Receiving Fetroja in Trial 1

Adverse reaction	Fetroja* (N=300]	Imipenem/cilastatin† (N=148)
Diarrhea	4%	6%
Infusion site reactions‡	4%	5%
Constipation	3%	4%
Rash§	3%	<1%
Candidiasis‖	2%	3%
Cough	2%	<1%
Elevations in liver tests¶	2%	<1%
Headache	2%	5%
Hypokalemia#	2%	3%
Nausea	2%	4%
Vomiting	2%	1%

cUTI=complicated urinary tract infection.
*2 grams intravenous over 1 hour every 8 hours (with dosing adjustment based on renal function)
†1 gram intravenous over 1 hour every 8 hours (with dosing adjustment based on renal function and body weight)
‡Infusion site reactions include infusion site erythema, inflammation, pain, pruritis, injection site pain, and phlebitis.
§Rash includes rash macular, rash maculopapular, erythema, skin irritation.
‖Candidiasis includes oral or vulvovaginal candidiasis, candiduria.
¶Elevations in liver tests include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood alkaline phosphatase, hepatic enzyme increased.
#Hypokalemia includes blood potassium decreased.

Other Adverse Reactions of Fetroja in the cUTI Patients (Trial 1)

The following selected adverse reactions were reported in Fetroja-treated cUTI patients at a rate of less than 2% in Trial 1.

Blood and lymphatic disorders: thrombocytosis

Cardiac disorders: congestive heart failure, bradycardia, atrial fibrillation

Gastrointestinal disorders: abdominal pain, dry mouth, stomatitis

General system disorders: pyrexia, peripheral edema

Hepatobiliary disorders: cholelithiasis, cholecystitis, gallbladder pain

Immune system disorders: drug hypersensitivity

Infections and infestations: *Clostridioides difficile* infection

Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), red blood cells urine positive, creatine phosphokinase increase

Metabolism and nutrition disorders: decreased appetite, hypocalcemia, fluid overload

Nervous system disorders: dysgeusia, seizure

Respiratory, thoracic, and mediastinal disorders: dyspnea, pleural effusion

Skin and subcutaneous tissue disorders: pruritis

Psychiatric disorders: insomnia, restlessness

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

Fetroja was evaluated in an active-controlled clinical trial in patients with HABP/VABP (Trial 2). In this trial, 148 patients received Fetroja 2 grams every 8 hours infused over 3 hours, and 150 patients received meropenem 2 grams every 8 hours infused over 3 hours. Doses of study treatments were adjusted based on renal function. The median age was 67 years, approximately 59% of patients were 65 years of age and older, 69% were male, and 68% were White. Overall, approximately 60% were ventilated at randomization, including 41% with VABP and 14% with ventilated HABP. The mean Acute Physiology And Chronic Health Evaluation (APACHE II) score was 16. All patients received empiric treatment for Gram-positive organisms with linezolid for at least 5 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 2, serious adverse reactions occurred in 54/148 (36.5%) HABP/VABP patients treated with Fetroja and 45/150 (30%) of HABP/VABP patients treated with meropenem. Adverse reactions leading to death were reported in 39/148 (26.4%) patients treated with Fetroja and 35/150 (23.3%) patients treated with meropenem. Adverse reactions leading to discontinuation of treatment occurred in 12/148 (8.1%) of patients treated with Fetroja and 14/150 (9.3%) of patients treated with meropenem. The most common adverse reactions leading to discontinuation in both treatment groups were elevated liver tests.

Common Adverse Reactions

Table 7 lists the most common selected adverse reactions occurring in ≥4% of patients receiving Fetroja in the HABP/VABP trial.

Table 7 Selected Adverse Reactions Occurring in ≥4% of HABP/VABP Patients Receiving Fetroja in Trial 2

Adverse Reaction	Fetroja* (N=148)	Meropenem† (N=150)
Elevations in liver tests‡	16%	16%
Hypokalemia§	11%	15%
Diarrhea	9%	9%
Hypomagnesemia	5%	<1%
Atrial fibrillation	5%	3%

HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.
*2 grams intravenous over 3 hours every 8 hours (with dosing adjustment based on renal function)
†2 grams intravenous over 3 hours every 8 hours (with dosing adjustment based on renal function)
‡Elevations in liver tests include the following terms: aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyl transferase increased, liver function test increased, liver function test abnormal, hepatic enzyme increased, transaminases increased, hypertransaminesemia.
§Hypokalemia includes blood potassium decreased.

Other Adverse Reactions of Fetroja in HABP/VABP Patients in Trial 2

The following selected adverse reactions were reported in Fetroja-treated HABP/VABP patients at a rate of less than 4% in Trial 2:

Blood and lymphatic disorders: thrombocytopenia, thrombocytosis
Cardiac disorders: myocardial infarction, atrial flutter
Gastrointestinal disorders: nausea, vomiting, abdominal pain
Hepatobiliary disorders: cholecystitis, cholestasis
Infections and infestations: *C difficile* infection, oral candidiasis
Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), and activated partial thromboplastin time (aPTT)
Metabolism and nutrition disorders: hypocalcemia, hyperkalemia
Nervous system disorders: seizure
Renal and genitourinary disorders: acute interstitial nephritis
Respiratory, thoracic, and mediastinal disorders: cough
Skin and subcutaneous tissue disorders: rash including rash erythematous

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

11. CONTRAINDICATIONS[1]:

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

12. WARNINGS AND PRECAUTIONS[1]:

Increase in All-Cause Mortality in Patients With Carbapenem-Resistant Gram-Negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with Fetroja as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with Fetroja than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *A baumannii* complex, *S maltophilia*, and *P aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in Fetroja-treated patients in clinical trials. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

Before therapy with Fetroja is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue Fetroja if an allergic reaction occurs.

Clostridioides difficile-associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Fetroja. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C difficile*.

C difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial drugs not directed against *C difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C difficile*, and institute surgical evaluation as clinically indicated.

Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including Fetroja, have been implicated in triggering seizures. Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust Fetroja dosing based on creatinine clearance. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether Fetroja should be discontinued.

Development of Drug-Resistant Bacteria

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

Please see Important Safety Information on pages 12 and 13 and Full Prescribing Information for Fetroja, or visit Fetroja.com.

13. DRUG INTERACTIONS[1]:

Drug/Laboratory Test Interactions

Cefiderocol may result in false-positive results in dipstick tests (urine protein, ketones, or occult blood). Use alternate clinical laboratory methods of testing to confirm positive tests.

14. USE IN SPECIFIC POPULATIONS[1]:

Pregnancy

Risk Summary

There are no available data on Fetroja use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Available data from published prospective cohort studies, case series, and case reports over several decades with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Developmental toxicity studies with cefiderocol administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses providing exposure levels 0.9 (rats) or 1.3 times (mice) higher than the average observed in patients receiving the maximum recommended daily dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with cephalosporin use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Developmental toxicity was not observed in rats at intravenous doses of up to 1000 mg/kg/day or mice at subcutaneous doses of up to 2000 mg/kg/day given during the period of organogenesis (gestation days 6-17 in rats and 6-15 in mice). No treatment-related malformations or reductions in fetal viability were observed. Mean plasma exposure (AUC) at these doses was approximately 0.9 times (rats) and 1.3 times (mice) the daily mean plasma exposure in patients that received 2 grams of cefiderocol infused intravenously every 8 hours.

In a pre- and postnatal development study, cefiderocol was administered intravenously at doses up to 1000 mg/kg/day to rats from Day 6 of pregnancy until weaning. No adverse effects on parturition, maternal function, or pre- and postnatal development and viability of the pups were observed.

In pregnant rats, cefiderocol-derived radioactivity was shown to cross the placenta, but the amount detected in fetuses was a small percentage (<0.5%) of the dose.

Lactation

Risk Summary

It is not known whether cefiderocol is excreted into human milk; however, cefiderocol-derived radioactivity was detected in the milk of lactating rats that received the drug intravenously. When a drug is present in animal milk, it is likely that the drug will be present in human milk. No information is available on the effects of Fetroja on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fetroja and any potential adverse effects on the breastfed child from Fetroja or from the underlying maternal condition.

Data

Cefiderocol-derived radioactivity was detected in milk following intravenous administration to lactating rats. The peak level in rat milk was approximately 6% of the peak plasma level.

Pediatric Use

Safety and effectiveness of Fetroja in pediatric patients younger than 18 years of age have not been established.

Geriatric Use

cUTI

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

HABP/VABP

Of the 148 patients treated with Fetroja in the HABP/VABP trial, 83 (56.1%) were 65 years of age and older, and 40 (27%) were 75 years of age and older.

The incidence of adverse reactions in patients treated with Fetroja was similar in patients under 65 years of age as compared to older patients (65 years of age and older and 75 years of age and older). The incidence of adverse reactions in older patients (65 years of age and older and 75 years of age and older) was also similar between treatment groups.

Clinical cure rates at the Test-of-Cure (TOC) visit in Fetroja-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age and 75 years of age and older were 60%, 77.5% and 60%, respectively. In comparison, the clinical cure rates at the TOC visit in the meropenem-treated patients for each of these subgroups were 65.5%, 64.4% and 70.5%, respectively. The observed all-cause mortality rates at Day 14 in the Fetroja-treated patients for each of these subgroups were 12.3%, 7.5% and 17.5%, respectively. In comparison, in the meropenem-treated patients for each of these subgroups, they were 10.3%, 17.8% and 9.1%, respectively.

cUTI and HABP/VABP

Fetroja is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. No dosage adjustment is required based on age. Dosage adjustment for elderly patients should be based on renal function.

Renal Impairment

Patients With CLcr 60 to 89 mL/min

No dosage adjustment of Fetroja is recommended in patients with CLcr 60 to 89 mL/min.

Patients With CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Dose adjustment is required in patients with CLcr less than 60 mL/min, and in patients who are receiving HD. In patients requiring HD, complete HD at the latest possible time before the start of cefiderocol dosing. Monitor renal function regularly and adjust the dosage of Fetroja accordingly as renal function may change during the course of therapy.

Patients Receiving CRRT

A total of 16 patients treated with Fetroja received CRRT in clinical trials. Dosage adjustment of Fetroja is required in patients receiving CRRT including CVVH, CVVHD, and CVVHDF. Dosage of Fetroja should be based on the effluent flow rate in patients receiving CRRT. While on CRRT, a patient's residual renal function may change. Improvements or reductions in residual renal function may warrant a change in Fetroja dosage.

Patients With CLcr 120 mL/min or Greater

CLcr 120 mL/min or greater may be seen in seriously ill patients, who are receiving intravenous fluid resuscitation. Dosage adjustment of Fetroja is required in patients with CLcr 120 mL/min or greater. Monitor renal function regularly and adjust the dosage of Fetroja accordingly as renal function may change during the course of therapy.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of cefiderocol have not been evaluated. Hepatic impairment is not expected to alter the elimination of cefiderocol as hepatic metabolism/excretion represents a minor pathway of elimination for cefiderocol. Dosage adjustments are not necessary in patients with impaired hepatic function.

INDICATIONS

Fetroja® (cefiderocol) is indicated in patients 18 years of age or older for the treatment of 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.

Fetroja is indicated in patients 18 years of age or older for the treatment of 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*.

USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Fetroja and other antibacterial drugs, Fetroja should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Please see additional Important Safety Information on next page and Full Prescribing Information for Fetroja, or visit Fetroja.com.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

WARNINGS AND PRECAUTIONS

Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with Fetroja as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with Fetroja than in patients treated with BAT [25/101 (24.8%) vs 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49 [34/101 (33.7%) vs 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in Fetroja-treated patients in clinical trials. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

Before therapy with Fetroja is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue Fetroja if an allergic reaction occurs.

***Clostridioides difficile*-associated Diarrhea (CDAD)**

Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Fetroja. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including Fetroja, have been implicated in triggering seizures. Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust Fetroja dosing based on creatinine clearance. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether Fetroja should be discontinued.

Development of Drug-Resistant Bacteria

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

ADVERSE REACTIONS

The most common adverse reactions occurring in (≥2%) of patients receiving Fetroja compared to imipenem/cilastatin in the cUTI trial were: diarrhea (4% vs 6%), infusion site reactions (4% vs 5%), constipation (3% vs 4%), rash (3% vs <1%), candidiasis (2% vs 3%), cough (2% vs <1%), elevations in liver tests (2% vs <1%), headache (2% vs 5%), hypokalemia (2% vs 3%), nausea (2% vs 4%), and vomiting (2% vs 1%). The most common adverse reactions occurring in (≥4%) of patients receiving Fetroja compared to meropenem in the HABP/VABP trial were: elevations in liver tests (16% vs 16%), hypokalemia (11% vs 15%), diarrhea (9% vs 9%), hypomagnesemia (5% vs <1%), and atrial fibrillation (5% vs 3%).

Please see Full Prescribing Information for Fetroja, or visit Fetroja.com.

References: 1. Fetroja [package insert]. Florham Park, NJ: Shionogi Inc.; 2020. **2.** US Food and Drug Administration website. https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019. Accessed November 15, 2019. **3.** US Food and Drug Administration website. https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibacterial-drug-treat-complicated-urinary-tract-infections-part-ongoing-efforts. Accessed November 15, 2019.

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Fetroja® (cefiderocol) for injection