

ICD-10-PCS Code Proposal: Fetroja[®] (cefiderocol) for injection

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SHIONOGI INC.

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Fetroja[®] (cefiderocol) Overview

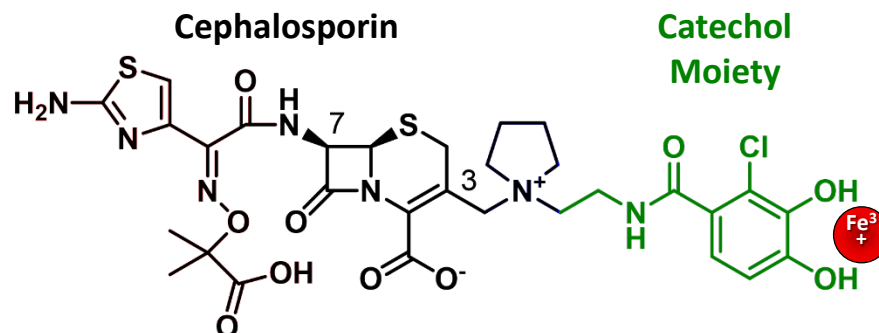
- Cefiderocol is a cephalosporin antibiotic that functions as a siderophore and binds to extracellular free ferric iron

- FDA designated cefiderocol as a Qualified Infectious Disease Product (QIDP): August 18, 2015
- FDA approval date: November 14, 2019

- Indication

Cefiderocol is indicated in patients 18 years of age or older who have limited or no alternative treatment options 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

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. Generally, deaths were in patients with infections caused by Gram-negative organisms, including nonfermenters such as *Acinetobacter baumannii*, *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. The safety and efficacy of Fetroja has not been established for the treatment of nosocomial pneumonia, bloodstream infections, or sepsis. Reserve Fetroja for use in patients who have limited or no alternative treatment options for the treatment of cUTI.



- Provides stability against most β -lactamases
- Binds to free iron

Disease Burden of cUTI

- 3 million complicated UTIs treated in hospital setting annually¹
- 400,000 hospitalizations each year in US²
- 50% increased incidence over past 15 years²
- 85% are caused by Gram-negative pathogens¹
- cUTI causes 10-30% of severe sepsis³
 - Mortality rate of $\geq 25\%$
- Carbapenem-resistant Gram-negative pathogens associated with increased mortality⁴

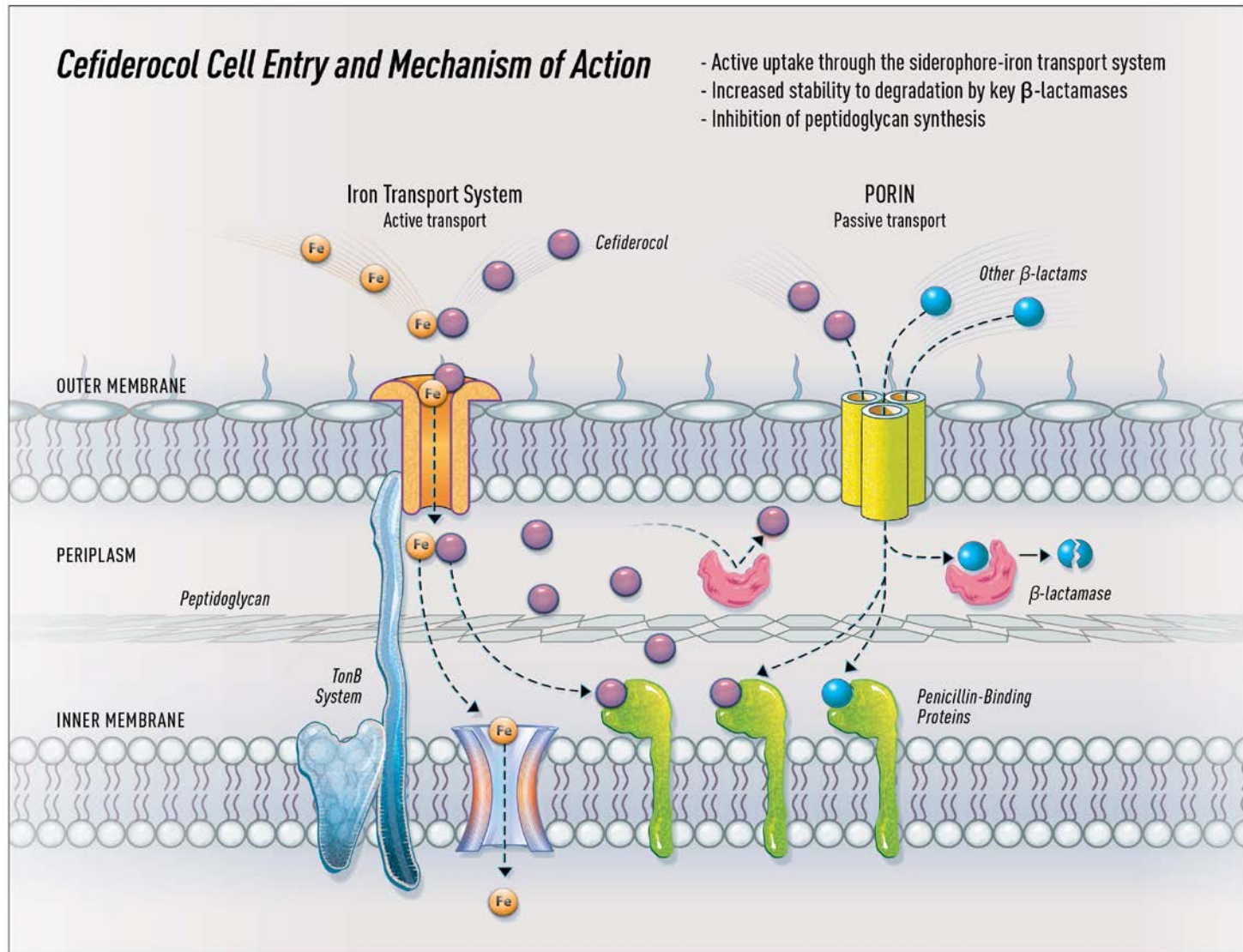
1. Flores-Mireles AL et al. *Nat Rev Micro* 2015;13:269-284.

2. Simmering JE et al. *Open For Inf Dis* 2016 DOI:10.1093/ofid/ofw281.

3. Peach BC et al. *Gerontol Geriatric Med* 2016 link.springer.com/chapter/10.1007/978-3-319-68276.

4. Zilberberg M et al. *BMC Infect Dis* 2017;17:279 DOI 10.1186/s12879-017-2383-z.

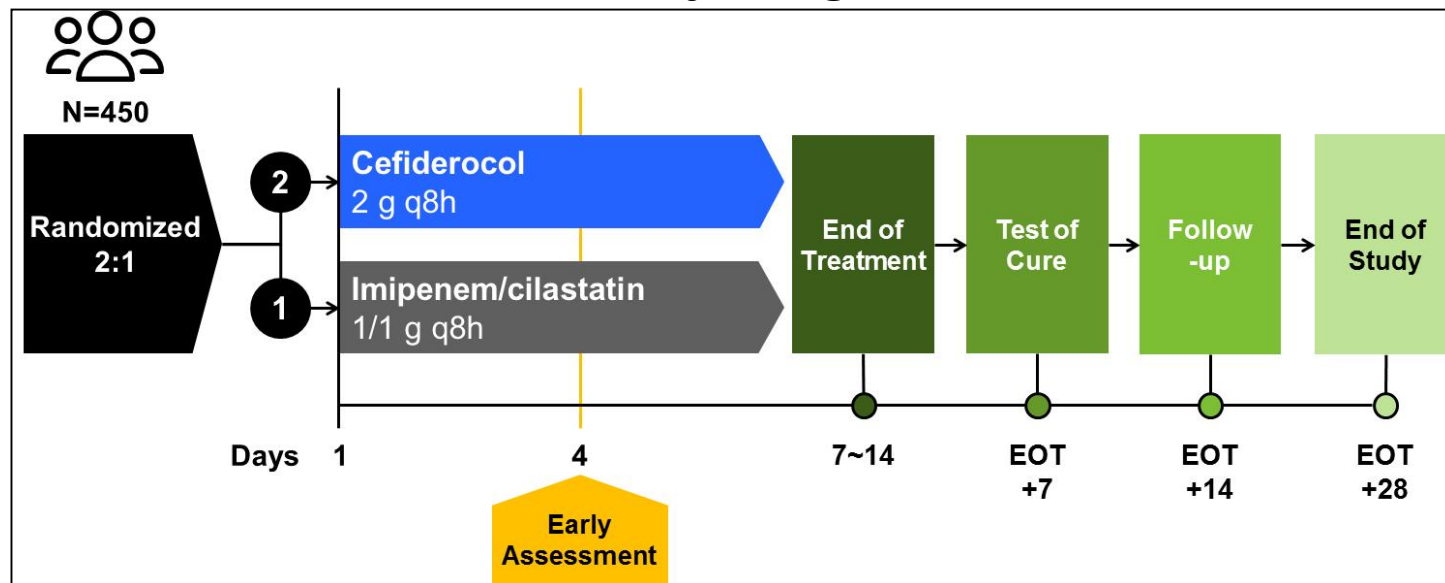
Fetroja Mechanism of Action



Cefiderocol APEKs cUTI Clinical Trial

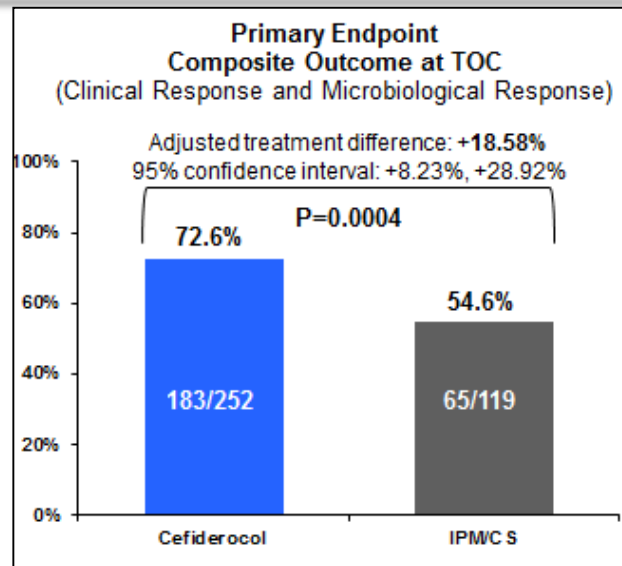
- Phase 2, randomized, double-blind, non-inferiority trial for cefiderocol versus imipenem-cilastatin (IPM/CS) for the treatment of cUTI caused by Gram-negative pathogens
- Results from the study demonstrated treatment with cefiderocol met non-inferiority versus IPM/CS in patients with cUTI at test of cure (TOC)

Study Design

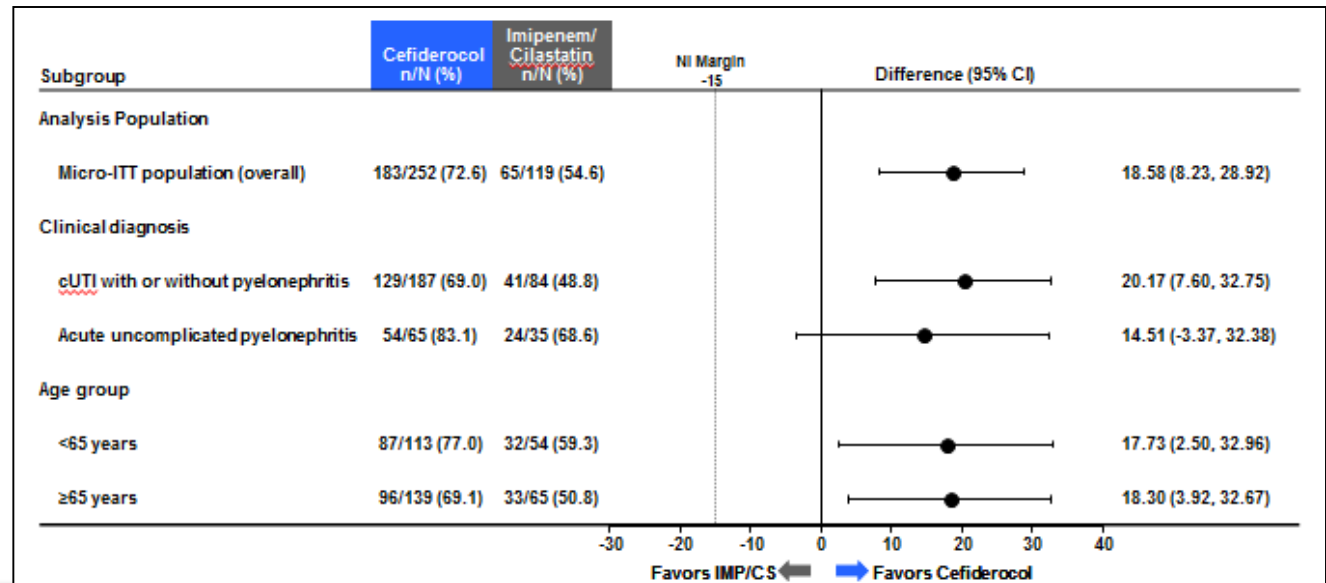


Cefiderocol APEKs cUTI Clinical Trial (cont'd)

Primary
Endpoint



Composite
Endpoint at
Test of Cure by
Subgroup



APEKs-cUTI Safety

Adverse Events with an Incidence >2% observed in patients taking cefiderocol

Adverse Event	Cefiderocol N=300 %	Imipenem/Cilastatin N=148 %
Diarrhea	4	6
Infusion site reactions ^a	4	5
Constipation	3	4
Rash ^b	3	<1
Candidiasis ^c	2	3
Cough	2	<1
Elevations in liver tests ^d	2	<1
Headache	2	5
Hypokalemia ^e	2	3
Nausea	2	4
Vomiting	2	1

^a Infusion site reactions include infusion site erythema, inflammation, pain, pruritis, injection site pain, and phlebitis.

^b Rash includes rash macular, rash maculopapular, erythema, skin irritation.

^c Candidiasis includes oral or vulvovaginal candidiasis, candiduria.

^d Elevations in liver tests include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood alkaline phosphatase, hepatic enzyme increased.

^e Hypokalemia includes blood potassium decreased.

References: 1. Fetroja [package insert]. Florham Park, NJ: Shionogi Inc.; 2019.

Cefiderocol Dosing

- Fetroja is supplied as a sterile, lyophilized powder that must be reconstituted and subsequently diluted using aseptic technique prior to intravenous infusion
- Recommended dosage and dosage adjustments of cefiderocol for adult patient

Estimated creatinine clearance (CLcr) ¹	Dose	Frequency	Infusion Time
60 to 119 mL/min (recommended dosage)	2 grams	Every 8 hours	3 hours
30 to 59 mL/min	1.5 grams	Every 8 hours	3 hours
15 to 29 mL/min	1 gram	Every 8 hours	3 hours
<15 mL/min (ESRD patients with or without intermittent HD ²)	0.75 gram	Every 12 hours	3 hours
≥ 120 mL/min	2 grams	Every 6 hours	3 hours

¹CLcr=creatinine clearance estimated by Cockcroft-Gault equation

²Cefiderocol is removed by HD; thus, complete HD at the latest possible time before the start of cefiderocol dosing.

ESRD=end-stage renal disease; HD=hemodialysis

References: 1. Fetroja [package insert]. Florham Park, NJ: Shionogi Inc.; 2019.

Summary

- cUTIs are the second leading cause of hospitalization in the elderly and have substantial morbidity and worse outcomes if the causative pathogens are carbapenem-resistant
- Cefiderocol has been designated as a Qualified Infectious Disease Product by the FDA
- FDA approval was received November 14, 2019
- Cefiderocol is indicated for cUTI
- Cefiderocol is currently being evaluated for an NTAP
- Specific ICD-10-PCS codes are required to track the utilization of cefiderocol in hospital inpatient cases

Appendix – Fetroja[®] (cefiderocol) Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FETROJA[®] safely and effectively. See full prescribing information for FETROJA.

FETROJA (cefiderocol) for injection, for intravenous use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

FETROJA is a cephalosporin antibacterial indicated in patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by susceptible Gram-negative microorganisms. (1.1)
Approval of this indication is based on limited clinical safety and efficacy data for FETROJA. (1.1, 14)

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 bacteria. (1.2)

DOSAGE AND ADMINISTRATION

- Administer 2 grams of FETROJA for injection every 8 hours by intravenous (IV) infusion over 3 hours in patients with creatinine clearance (CLcr) 60 to 119 mL/min. (2.1)
- Dose adjustments are required for patients with CLcr less than 60 mL/min and for patients with CLcr 120 mL/min or greater. (2.2)
- See full prescribing information for instructions on preparation of FETROJA doses. (2.3)
- See full prescribing information for drug compatibilities. (2.4)

DOSAGE FORMS AND STRENGTHS

For injection: 1 gram of cefiderocol as a lyophilized powder for reconstitution in single-dose vials. (3)

CONTRAINDICATIONS

FETROJA is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol and other beta-lactam antibacterial drugs or other components of FETROJA. (4)

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 FETROJA-treated patients compared to those treated with best available therapy (BAT). Reserve FETROJA for use in patients who have limited or no alternative treatment options for the treatment of cUTI. Closely monitor the clinical response to therapy in patients with cUTI. (5.1)
- Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed with FETROJA. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue FETROJA. (5.2)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including FETROJA. Evaluate if diarrhea occurs. (5.3)
- Seizures and Other Central Nervous System (CNS) Adverse Reactions: CNS adverse reactions such as seizures have been reported with FETROJA. If focal tremors, myoclonus, or seizures occur, evaluate patients to determine whether FETROJA should be discontinued. (5.4)

ADVERSE REACTIONS

The most frequently occurring adverse reactions in greater than or equal to 2% of patients treated with FETROJA were diarrhea, infusion site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, headache, hypokalemia, nausea, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-800-849-9707 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use alternate testing methods to confirm positive results of dipstick tests (urine protein, ketones, or occult blood). (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2019