Fetroja – Use in Patients With Hypersensitivity or Cross-Sensitivity to β-lactam Antibiotics

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Summary | Clinical Studies | Real-World Evidence | Relevant Prescribing Information | Literature Search | Abbreviations, References

Summary

- In the cefiderocol Phase 2 and Phase 3 studies, patients were excluded if they had a documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam (note: for β-lactams, a history of a mild rash followed by uneventful re-exposure was not a contraindication to enrollment)[1-3]

- In the Phase 2 **APEKS-cUTI** study, 7 (2.3%) patients in the cefiderocol group (safety population) had a documented medical history of drug hypersensitivity, but the drug class was not specified[1]
  - Drug hypersensitivity (itching) occurred in 1 (0.3%) patient in the cefiderocol group, however there was no rash observed. The patient, who did not have a history of allergies to β-lactam antibiotics, discontinued the study drug due to hypersensivity[1,4]

- In the Phase 3 **APEKS-NP** study, 5 (3.4%) patients in the cefiderocol group had a documented medical history of drug hypersensitivity, but the drug class was not specified[5]

  - In the safety population, there were no reports of drug hypersensitivity in the cefiderocol group[5]
  - Rash occurred in 1 (0.7%) patient in the cefiderocol group, which was deemed to be drug-related[2,4,5]

- In the Phase 3 **CREDIBLE-CR** study, 2 (2%) patients in the cefiderocol group had a documented medical history of penicillin drug allergy. Neither patient experienced a hypersensitivity adverse event (AE)[6]

- **El Ghali et al (2024)** conducted a multicenter, retrospective study of 112 patients receiving ≥72 hours of cefiderocol and found that 17 patients with a prior history of β-lactam allergy experienced no allergic reaction to cefiderocol[7]
  - 2 patients, both with a prior history of penicillin allergy, developed a non-anaphylactic rash

- Although cefiderocol resembles the chemical structure of ceftazidime and cefepime[8], studies have not been conducted to evaluate the cross reactivity of cefiderocol with these cephalosporins that possess similar side chains

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Summary | Clinical Studies | Real-World Evidence | Relevant Prescribing Information | Literature Search | Abbreviations, References

APEKS-cUTI | APEKS-NP | CREDIBLE-CR

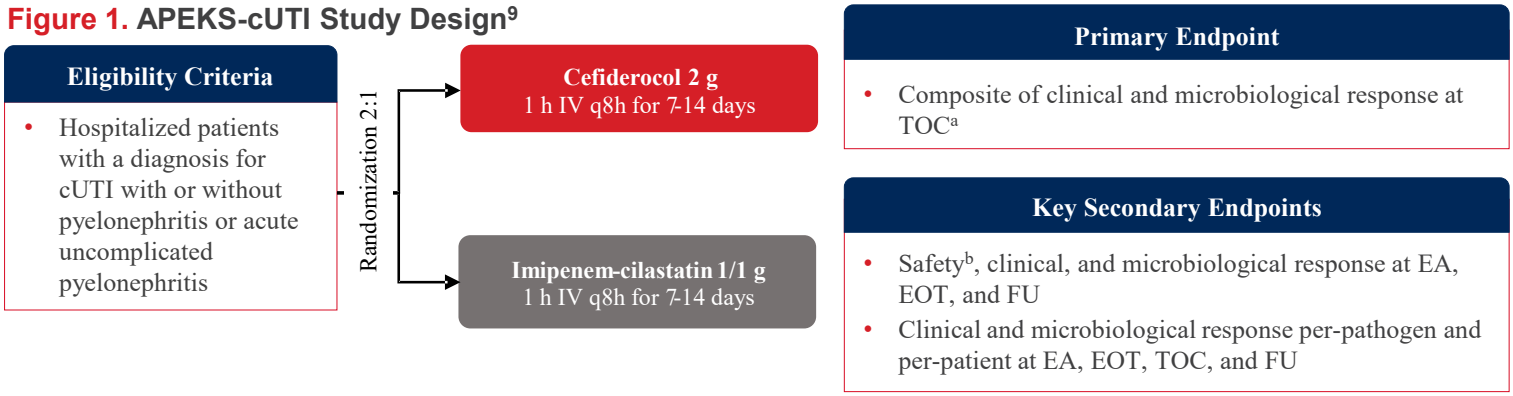
Clinical Studies

Phase 2 Clinical Study

APEKS-cUTI

- APEKS-cUTI (NCT02321800) was a Phase 2, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in complicated urinary tract infections (cUTI) caused by suspected Gram-negative pathogens[9]

Figure 1. APEKS-cUTI Study Design[9]



Abbreviations: CFU, colony-forming unit; cUTI, complicated urinary tract infection; EA, early assessment; EOT, end of treatment; FU, follow-up; IV, intravenous; g, grams; h, hours; mITT, modified intention-to-treat; q8h, every 8 hours; TOC, test of cure.

[a]In the mITT population (noninferiority margin, -15%), defined as all randomly assigned individuals who received at least 1 dose of study drug and had qualifying Gram-negative uropathogen (≥1×10^5 CFU/mL).

[b]Safety assessed in all randomly assigned individuals who received at least 1 dose of study drug, according to the treatment they received. Adverse events were monitored daily during treatment administration in the hospital.

The modified intention-to-treat (mITT) population consisted of 371 patients (252 patients in the cefiderocol group and 119 patients in the imipenem-cilastatin group).[9]

- A medical history of drug hypersensitivity was reported in 7 (2.3%) patients in the cefiderocol group (safety population), though the drug class was not specified[1]
  - The safety and efficacy of cefiderocol was not evaluated in this specific sub-population
- Drug hypersensitivity (itching) occurred in 1 (0.3%) patient in the cefiderocol group, however there was no rash observed. The patient, who did not have a history of allergies to β-lactam antibiotics, discontinued the study drug due to hypersensivity[1,4]
- Rash was reported in 5 (1.7%) patients in the cefiderocol group. None of these events were related to cefiderocol[1,4]

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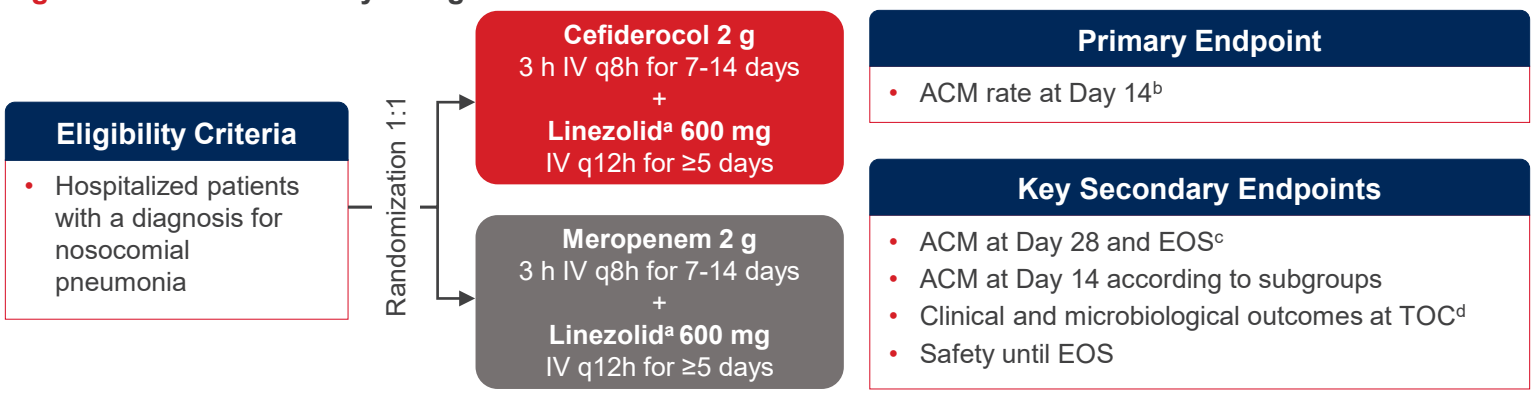
Clinical Studies

Phase 3 Clinical Studies

APEKS-NP

- APEKS-NP (NCT03032380) was a Phase 3, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by suspected Gram-negative pathogens[10]

Figure 2. APEKS-NP Study Design[10]



Abbreviations: ACM, all-cause mortality; EOS, end of study; IV, intravenous; g, grams; h, hours; mITT, modified intention-to-treat; q8h, every 8 hours; q12h, every 12 hours; RTI, respiratory tract infection; TOC, test of cure.
[a]Administered to cover Gram-positive bacteria.
[b]In the mITT population (noninferiority margin, -12.5%), defined as all randomized patients who received ≥1 dose of a study drug and had evidence of a Gram-negative lower RTI.
[c]EOT + 28 days (±3 days).
[d]EOT + 7 days (±2 days).

The intention-to-treat (ITT)/safety population consisted of 298 patients (148 patients in the cefiderocol group and 150 patients in the meropenem group).[10]

- A medical history of drug hypersensitivity was reported in 5 (3.4%) patients in the cefiderocol group (safety population), though the drug class was not specified[5]
  - The safety and efficacy of cefiderocol was not evaluated in this specific sub-population[5]
- Rash occurred in 1 (0.7%) patient in the cefiderocol group, which was deemed to be drug-related[2,4,5]
- There were no reports of drug hypersensitivity in the cefiderocol group[5]

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Summary | Clinical Studies | Real-World Evidence | Relevant Prescribing Information | Literature Search | Abbreviations, References

APEKS-cUTI | APEKS-NP | CREDIBLE-CR

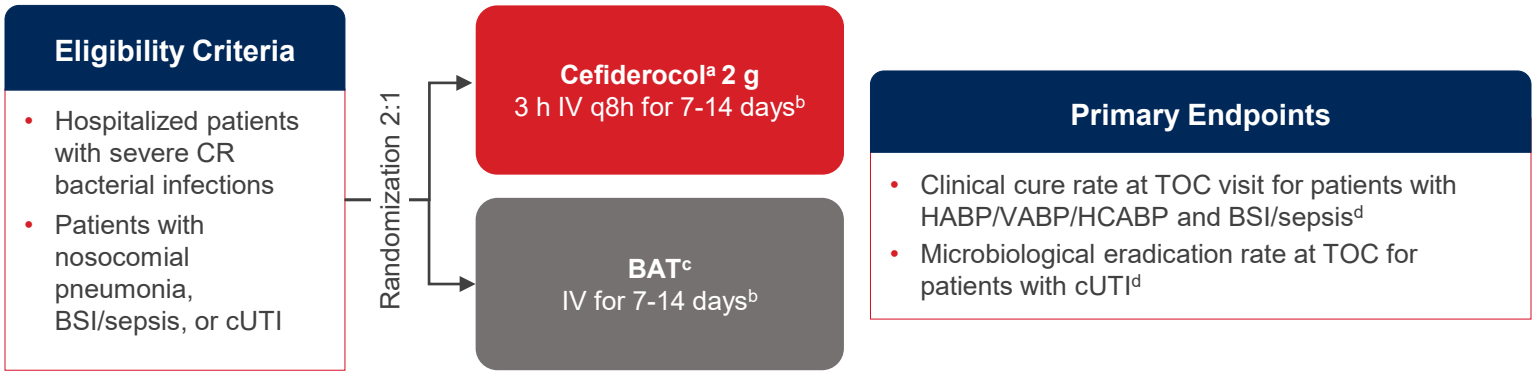
Clinical Studies

Phase 3 Clinical Studies

CREDIBLE-CR

- CREDIBLE-CR (NCT02714595) was a Phase 3, prospective, open-label, multicenter, randomized, parallel-group, descriptive study that assessed the efficacy and safety of cefiderocol and best available therapy (BAT) in hospitalized patients with severe CR bacterial infections[11]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[11]

Figure 3. CREDIBLE-CR Study Design[11]



Abbreviations: BAT, best available therapy; BSI, bloodstream infection; CR, carbapenem-resistant; cUTI, complicated urinary tract infection; IV, intravenous; g, grams; h, hours; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; q8h, every 8 hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.
[a]Could be complemented with one adjunctive antibiotic therapy, excluding polymyxins, cephalosporins, and carbapenems and combinations with a β-lactamase inhibitor.
[b]Could be extended up to 21 days at the discretion of the investigator.
[c]Selected before randomization and could consist of up to 3 systemic antibiotics.
[d]Defined as all patients with a confirmed CR Gram-negative pathogen who received at least 1 dose of study drug.

The ITT/safety population consisted of 150 patients (101 patients in the cefiderocol group and 49 patients in the BAT group).[11]

- Of the 101 patients who received cefiderocol, a total of 2 (2%) patients had a medical history of allergy to penicillin: 1 patient with a possible penicillin allergy and another patient with an allergy to penicillin and amoxicillin/clavulanic acid[6]
  - Of the 2 patients, neither experienced an adverse event of hypersensitivity reaction after receiving treatment with cefiderocol[6]
- 1 (1%) patient in the cefiderocol group experienced an adverse event of hypersensitivity.[4,6] This patient had a medical history of allergy to phenytoin[6]
- Rash occurred in 3 (3%) patients in the cefiderocol group[6]
  - Drug-related rash occurred in 1 (1%) patient in the cefiderocol group[4,6]

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Real-World Evidence

El Ghali et al (2024) reported a retrospective analysis of real-world data from 6 US medical centers and assessed outcomes for 112 adults who received ≥72 hours of cefiderocol from January 2018 to May 2023.[7]

- Overall, 110 (98.2%) patients had a CR infection; *P. aeruginosa* was the most common pathogen identified in 61 (54.5%) patients followed by *A. baumannii* in 32 (28.6%) patients
- The median (IQR) duration of cefiderocol treatment was 9 (6-13) days
- Combination therapy with cefiderocol was administered to 39 (34.8%) patients; Colistin-polymyxin was the most frequent concomitant agent administered in 8 (7.1%) patients followed by ceftazidime-avibactam in 7 (6.3%) and aminoglycosides in 6 (5.4%) patients

Safety

- 2 patients, both with a history of allergies to penicillin, developed a non-anaphylactic rash during cefiderocol treatment[7]
- 17 patients with a history of β-lactam allergy, ranging from hives and itching to anaphylaxis and angioedema, received cefiderocol and experienced no allergic reactions during treatment[7]

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Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[12]

- Complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms:
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
  - *Pseudomonas aeruginosa*
  - *Enterobacter cloacae* complex
- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms:
  - *Acinetobacter baumannii* complex
  - *Escherichia coli*
  - *Enterobacter cloacae* complex
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other β-lactam antibacterial drugs, or any other component of Fetroja.[12]

As stated in **Section 5.2 Hypersensitivity Reactions** of the Fetroja **Full Prescribing Information**[12]:

> Hypersensitivity Reactions
> Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving β-lactam antibacterial drugs. Hypersensitivity was observed in Fetroja clinical trials. These reactions are more likely to occur in individuals with a history of β-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 β-lactam antibacterial drugs. Discontinue Fetroja if an allergic reaction occurs.

Please read the attached Fetroja **Full Prescribing Information.**

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Literature Search

As of September 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified an additional relevant reference regarding the use of cefiderocol in patients with hypersensitivity or cross-sensitivity to β-lactam antibiotics. For your review, these references are listed in the bibliography that follows:

- Young H, Michaelis LJ, Meyer R. Desensitisation programmes — pharmacy involvement in children presenting with allergies having an allogenic hematopoietic stem cell transplant. Poster presented at: EBMT; March 30-April 02, 2025; Florence, Italy

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from it should not be considered all-inclusive.

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ACM	all-cause mortality
AUP	acute uncomplicated pyelonephritis
BAT	best available therapy
BSI	bloodstream infection
CR	carbapenem-resistant
cUTI	complicated urinary tract infection
EA	early assessment
EOS	end of study
EOT	end of treatment
FU	follow-up
g	Gram
h	hour
HABP	hospital-acquired bacterial pneumonia
HCABP	healthcare-associated bacterial pneumonia
ITT	intention-to-treat
IV	intravenous
mITT	modified intention-to-treat
q12h	every 12 hours
q8h	every 8 hours
TOC	test of cure
VABP	ventilator-associated bacterial pneumonia

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1. Data on File 1. Shionogi Inc., Florham Park, NJ, USA.
2. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis.* 2020. Suppl 1:S1-55. doi:10.1016/S1473-3099(20)30731-3
3. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis.* 2020. Suppl 1:S1-52. doi:10.1016/S1473-3099(20)30796-9
4. Matsunaga Y, Sonoyama T, Casanova L, et al. Safety profile of the novel siderophore cephalosporin cefiderocol in randomized phase 2 and phase 3 clinical studies of serious Gram-negative infections. Poster presented at: ID Week 2020. October 21 - 25, 2020. Virtual Conference, Online
5. Data on File 3. Shionogi Inc., Florham Park, NJ, USA.
6. Data on File 4. Shionogi Inc., Florham Park, NJ, USA.
7. El Ghali A, Kunz Coyne AJ, Lucas K, et al. Cefiderocol: early clinical experience for multi-drug resistant Gram-negative infections. *Microbiol Spectr*. 2024;12(2):e0310823. doi:10.1128/spectrum.03108-23
8. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and in vivo profiles of a novel siderophore cephalosporin. *Clin Infect Dis*. 2019;69(Suppl 7):S538-S543. doi:10.1093/cid/ciz826
9. Portsmouth S, van Veenuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis.* 2018;18(12):1319-1328. doi:10.1016/S1473-3099(18)30554-1
10. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. 2020. doi:10.1016/S1473-3099(20)30731-3.
11. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2020. doi:10.1016/S1473-3099(20)30796-9
12. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.