Fetroja® – Administration Less Than 3 Hours

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Summary

- **APEKS-cUTI**, a Phase 2, randomized, double-blind, non-inferiority study compared cefiderocol to imipenem–cilastatin for the treatment of cUTI. Patients were given a 1 h infusion of either cefiderocol 2 g or imipenem–cilastatin 1 g q8h for 7–14 days[1]
  - The primary endpoint (composite of clinical and microbiological response at TOC) was met in 183/252 (73%) patients in the cefiderocol group and 65/119 (55%) patients in the imipenem-cilastatin group
- **Gastalver-Martin et al (2023)** performed a retrospective study in 3 patients with COVID-19 and pan-resistant *Pseudomonas aeruginosa* between September 2020 and December 2021. Cefiderocol was administered as a loading dose of 2 g over 30 minutes, followed by a maintenance dose according to renal function[2]
  - Of the 3 patients evaluated, 1 achieved clinical cure, 1 died, and 1 developed resistance to cefiderocol
- **Katsube et al (2014)** performed a PK model which demonstrated that the PTA for cefiderocol 2 g q8h for either 50% or 75% of time at which free drug concentration in plasma exceeds MIC over dosing interval ($f_{T>MIC}$) was higher as a 3 h infusion than as a 1 h infusion[3]
- **Tsuji et al (2014)** evaluated a rat lung infection model with recreated humanized exposure profile against 3 strains of KPC and 2 strains of NDM-1 producing *Klebsiella pneumoniae*[4]
  - Cefiderocol 3 h infusion reduced *K. pneumoniae* below the limit of detection regardless of resistance phenotype (NDM-1 or KPC). The 1 h infusion demonstrated little to no efficacy against 4 of the strains
- **Matsumoto et al (2017)** evaluated rat RTI models simulating human plasma PK and found reductions in bacterial count ranged from 3.04 to 4.41 $\log_{10}$ CFU against all 5 CR isolates for cefiderocol 2 g q8h as a 3 h infusion. Reductions of 0.7 to 3.7 $\log_{10}$ CFU of 5 CR isolates were observed for cefiderocol 2 g q8h as a 1 h infusion[5]
- **Tsuji et al (2015)** performed an *in vitro* PD model in which both 1 h and 3 h infusions of cefiderocol demonstrated bactericidal activity (>3 $\log_{10}$ reduction) against 8 MDR strains[6]
- The recommended dosage of Fetroja (cefiderocol) is 2 g administered q8h by IV infusion over 3 h in adults with a CrCl of 60 to 119 mL/min[7]

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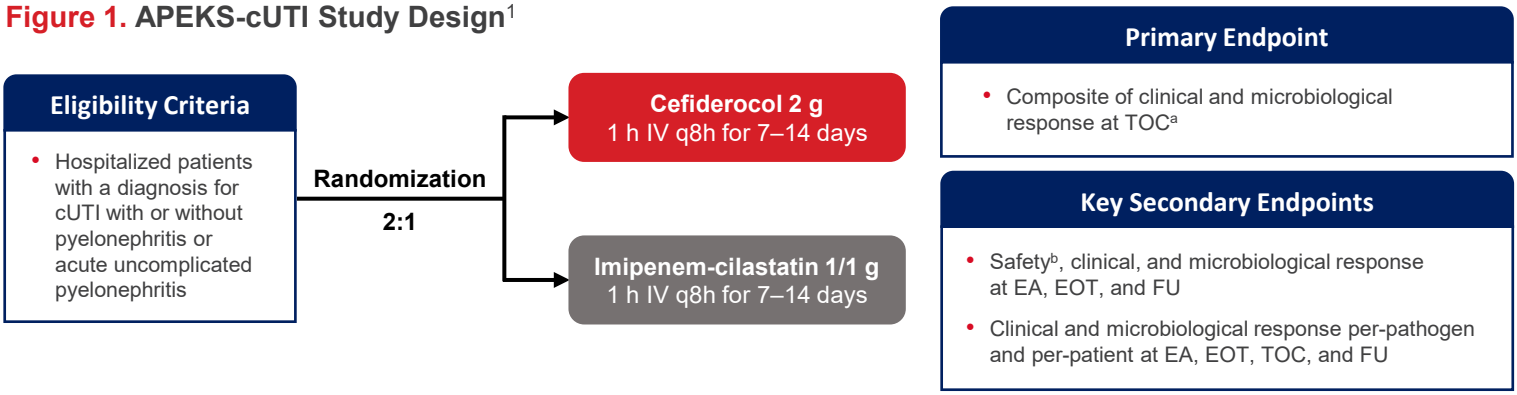
Clinical Study

APEKS-cUTI

A Phase 2, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in cUTI caused by suspected Gram-negative pathogens.[1]

- In the cefiderocol group and imipenem–cilastatin group, 252 and 119 patients had a qualifying Gram-negative uropathogen (≥1x10^5 CFU/mL), respectively, and were included in the mITT population[1]

Figure 1. APEKS-cUTI Study Design[1]



Abbreviations: CFU, colony-forming unit; cUTI, complicated urinary tract infection; EA, early assessment; EOT, end of treatment; FU, follow-up; g, grams; h, hours; IV, intravenous; mITT, modified intention-to-treat; q8h, every 8 hours; TOC, test of cure.
[a]In the mITT population (non-inferiority margin, -15%), defined as all randomly assigned individuals who received ≥1 dose of study drug and had qualifying Gram-negative uropathogen (≥1x10^5 CFU/mL). [b]Safety assessed in all randomly assigned individuals who received ≥1 dose of study drug, according to the treatment they received. AEs were monitored daily during treatment administration in the hospital.

Results[1]

- The primary efficacy endpoint was attained by 183 (73%) patients in the cefiderocol group and 65 (55%) patients in the imipenem-cilastatin group at TOC in the mITT population with an adjusted treatment difference of 18.58% (95% CI, 8.23 to 28.92; *P*=0.0004) favoring cefiderocol
  - This met the criteria for non-inferiority at the pre-specified 20% and 15% margins
- The proportion of patients who had a microbiological response was higher in the cefiderocol group than in the imipenem–cilastatin group (184 [73%] and 67 [56%], respectively; difference 17.25%, 6.92 to 27.58)
- The proportion of patients who had a clinical response was similar between the 2 groups (226 [90%] cefiderocol patients and 104 [87%] imipenem–cilastatin patients, respectively; difference 2.39%, –4.66 to 9.44)
- AEs were reported in 122/300 (41%) patients in the cefiderocol group, and 76/148 (51%) patients in the imipenem–cilastatin group, respectively
  - The majority of AEs were considered mild or moderate in severity, with GI disorders such as diarrhea and constipation being the most commonly reported events
- SAEs were reported in 14/300 (5%) patients in the cefiderocol group, and 12/148 (8%) patients in the imipenem–cilastatin group, respectively
  - The most common SAE was *Clostridioides difficile* colitis, occurring in 1 (<1%) patient in the cefiderocol group and 2 (1%) patients in the imipenem–cilastatin group

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Retrospective Study

Gastalver-Martin et al (2023) reported clinical results of 3 critically ill patients with COVID-19 pneumonia and pan-resistant *P. aeruginosa*, treated with cefiderocol. All patients had obesity, hypertension, and diabetes mellitus. The observational retrospective study was conducted from September 2020 to December 2021 and analyzed days admitted in the ICU, concomitant treatment, and the dosage/duration/results of cefiderocol treatment.[2]

- Cultures were resistant to all tested antibiotics and were susceptible to only cefiderocol and colistin
- Cefiderocol was administered as a loading dose of 2 g over 30 minutes, followed by maintenance dosing according to renal function over ≥3 h and in combination with colistin
  - The average treatment duration was 20.5±4.5 days
- 1 patient achieved clinical cure, 1 patient developed resistance to cefiderocol, and 1 patient died

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PK and PD Study

Phase 1 Clinical Study Data – PK Simulation

Katsube et al (2014) developed a PK model to depict the time courses of cefiderocol concentrations in plasma and urine and to predict efficacy for optimizing dosage regimens. Plasma and urine concentration data of cefiderocol following single doses, 100 to 2000 mg, or multiple doses, 1000 and 2000 mg IV infusions dosed q8h, were obtained from a Phase 1 study conducted in 54 healthy volunteers in Japan.[3]

- The plasma and urine data were fitted to a 3-compartment disposition model by a non-linear mixed effect model approach. The probability that $f_{T>MIC}$ reached 50% (a static effect in animal models) or 75% (1-$\log_{10}$ reduction in animal models) was calculated utilizing Monte Carlo simulation
  - The model used cefiderocol at 1 or 2 g infused over 1 or 3 h against MICs of 0.25–16 µg/mL. Simulations were performed to calculate the PTA

Results[3]

- The simulated median plasma concentration profile at steady state following 3 h infusion of cefiderocol 2 g q8h was sustainable compared to that of the 1 h infusion
- The PTA for cefiderocol 2 g q8h dose with 1 h infusion time was >90% at MICs up to 8 and 4 µg/mL for 50% and 75% of $f_{T>MIC}$, respectively
- The PTA for either 50% or 75% $f_{T>MIC}$ target at 2 g q8h was higher with the 3 h infusion compared to the 1 h infusion
- The MIC at which 90% of the isolates were inhibited (MIC_{90}) was 0.5, 2, 2, and 8 µg/mL against CR *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter baumannii*, respectively. Table 1 shows the PTA at dosage regimens of cefiderocol

Table 1. PTA* at Certain Dosage Regimens of Cefiderocol[3]

Dosage	Infusion Time	Regimen	Target $f_{T>MIC}$ (%)	MIC (µg/mL)						
				0.25	0.5	1	2	4	8	16
1 g	1 h	q12h	50	100*	100*	99.7*	86.2	9.3	0	0
			75		95.3*	51.5	3.6	0	0	0
		q8h				100*	100*	88.4	10.3	0
						95.7*	52.3	3.9	0	0
2 g	1 h	q12h				00*	100*	96.2*	7.1	0
						00*	89.9	15	0	0
		q8h				100*	100*	100*	95.7*	7
						100*	100*	90.7*	14.8	0
	3 h	q8h	50	100*	100*	100*	100*	100*	100*	55.5
			75	100*	100*	100*	100*	99.9*	65.3	0.6

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PK and PD Study

Table 1. PTA* at Certain Dosage Regimens of Cefiderocol[3]

Dosage	Infusion Time	Regimen	Target $f_{T>MIC}$ (%)	MIC (µg/mL)						
				0.25	0.5	1	2	4	8	16
1 g	1 h	q12h	50	100*	100*	99.7*	86.2	9.3	0	0
			75	99.7*	95.3*	51.5	3.6	0	0	0
		q8h	50	100*	100*	100*	100*	88.4	10.3	0
			75	100*	100*	95.7*	52.3	3.9	0	0
2 g	1 h	q12h	50	100*	100*	100*	100*	96.2*	7.1	0
			75	100*	100*	100*	89.9	15	0	0
		q8h	50	100*	100*	100*	100*	100*	95.7*	7
			75	100*	100*	100*	100*	90.7*	14.8	0
	3 h	q8h	50	100*	100*	100*	100*	100*	100*	55.5
			75	100*	100*	100*	100*	99.9*	65.3	0.6

Abbreviations: $f_{T>MIC}$, time at which free drug concentration in plasma exceeds MIC over dosing interval; g, gram(s); h, hour(s); MIC, minimum inhibitory concentration; PTA, probability of target attainment; q8h, every 8 hours; q12h, every 12 hours.
*PTA >90%.
Table adapted from Katsube et al. IDWeek. 2014.

respectively. Table 1 shows the PTA at dosage regimens of cefiderocol

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Pre-Clinical Studies

Animal Studies

Efficacy against *K. pneumoniae* Strains

Tsuji et al (2014) evaluated the efficacy of cefiderocol 2 g (as a 1 h and 3 h infusion) against 3 strains of KPC-producing and 2 strains of NDM-1-producing *K. pneumoniae* in a rat lung infection model with recreated human PK profiles. The exposure from a 1 h infusion was derived from the PK profile of cefiderocol 2 g infused over 1 h in a Phase 1 study of healthy volunteers and the exposure from a 3 h infusion was predicted using a computerized system.[4]

- The 3 h infusion reduced bacteria below the limit of detection in almost every animal, regardless of resistance phenotype (NDM-1 or KPC)
- The 1 h infusion demonstrated little to no efficacy against 4 of the 5 strains
- **Figure 2** provides a summary of the bacterial reductions obtained in each organism

Figure 2. Efficacy against NDM-1 and KPC-Producing *K. pneumoniae* in RTIs in Cannulated Rats[4]

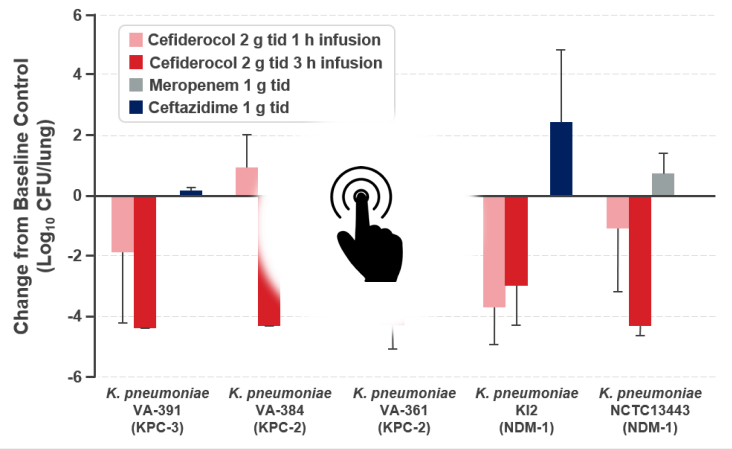


Table 2. Extrapolated $\%f_{T>MIC}$ with Simulated Cefiderocol 2 g tid[4]

Cefiderocol MIC (µg/mL)	$\%f_{T>MIC}$ (Rat)	
	1 h Infusion	3 h Infusion
0.125	100	100
0.25	[illegible]	100
0.5	[illegible]	100
1	[illegible]	100
2	[illegible]	100
4	[illegible]	100
8	[illegible]	100
16	[illegible]	81
32	25	31

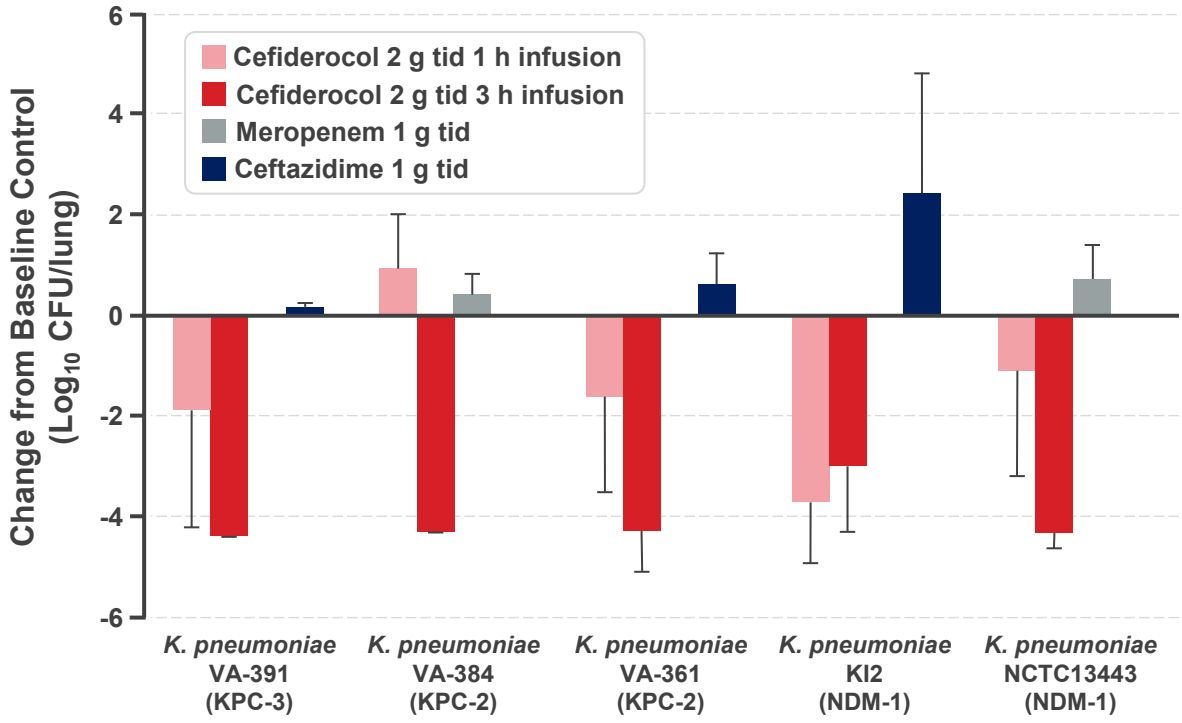
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Pre-Clinical Studies

Figure 2. PTA* at Certain Dosage Regimens of Cefiderocol[4]



Abbreviations: CFU, colony-forming units; g, gram(s); h, hour(s); KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; RTI, respiratory tract infection; tid, 3 times daily.
Figure adapted from Tsuji et al. IDWeek. 2014.

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Pre-Clinical Studies

Table 2. Extrapolated $\%f_{T>MIC}$ with Simulated Cefiderocol 2 g tid[4]

Cefiderocol MIC (µg/mL)	$\%f_{T>MIC}$ (Rat)	
	1 h Infusion	3 h Infusion
0.125	100	100
0.25	100	100
0.5	100	100
1	100	100
2	100	100
4	75	100
8	50	100
16	41	81
32	25	31

Abbreviations: $\%f_{T>MIC}$, the percentage of a dosage interval in which the free drug level exceeds the MIC; g, gram(s); h, hour(s); MIC, minimum inhibitory concentration; tid, three times daily.
Figure adapted from Tsuji et al. IDWeek. 2014.

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Pre-Clinical Studies (Cont.)

Efficacy against MDRP, MDRA, and CRKP

Matsumoto et al (2017) evaluated the efficacy of cefiderocol against MDRP, MDRA, and CRKP in rat RTI models simulating human plasma PK. For the subsequent *in vivo* studies, 5 MDR isolates (1 MDRP, 2 MDRA, 2 CRKP) and 1 cephalosporin-susceptible isolate (*P. aeruginosa* ATCC27853) were selected from global clinical isolates. MDR was defined as resistance to ceftazidime, imipenem and ciprofloxacin.[5]

- MICs for cefiderocol were determined via ID-CAMHB and MICs for ceftazidime and meropenem were determined by microdilution according to CLSI guidelines
- The PK profile observed in healthy subjects after dosing with 1 h infusions of cefiderocol 2 g q8h for 96 h was recreated in infected rats. The human PK profile for the 3 h cefiderocol infusion was simulated from the PK parameters for a 1 h infusion using 2-compartment model analysis

Results[5]

- Cefiderocol MICs for the test strains were between 0.125 to 8 µg/mL, as seen in **Table 3**
- After 96 h of antimicrobial treatment, reductions of 0.7 to 3.7 $\log_{10}$ CFU in the counts of 5 CR isolates (including *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*) were observed in the rats recreating the human PK for cefiderocol 2 g q8h as a 1 h infusion
- In the rats recreating the simulated 3 h infusion, reductions ranged from 3.04 to 4.41 $\log_{10}$ CFU against all 5 CR isolates

Table 3. MICs (µg/mL) of Cefiderocol, Ceftazidime, and Meropenem against Test Isolates[5]

Isolate	Phenotype and/or Carbapenemase	MIC (µg/mL)		
		[illegible]	Ceftazidime	Meropenem
P. aeruginosa				
ATCC 27853	Ceftazidime-susceptible		2	0.25
SR27001	MDR, IMP-1		>32	>32
A. baumannii				
1485176	MDR, OXA-51-like		>32	32
1485247	MDR, OXA-51-like		>32	8
K. pneumoniae				
VA-361	CR, KPC-2		>32	16
KI2	CR, NDM-1	8	>32	>32

Table 4. Extrapolated $\%f_{T>MIC}$ Achieved with Human Exposure of Cefiderocol 2 g q8h as a 1 h or 3 h Infusion in Infected Rats[5]

Cefiderocol MIC (µg/mL)	$\%f_{T>MIC}$	
	[illegible]	3 h Infusion
0.125		100
0.25		100
0.5		100
1		100
2		100
4		100
8	50	100

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Pre-Clinical Studies (Cont.)

Table 3. MICs (µg/mL) of Cefiderocol, Ceftazidime, and Meropenem against Test Isolates[5]

Isolate	Phenotype and/or Carbapenemase	MIC (µg/mL)		
		Cefiderocol	Ceftazidime	Meropenem
P. aeruginosa				
ATCC 27853	Ceftazidime-susceptible	0.5	2	0.25
SR27001	MDR, IMP-1	2	>32	>32
A. baumannii				
1485176	MDR, OXA-51-like	0.125	>32	32
1485247	MDR, OXA-51-like	2	>32	8
K. pneumoniae				
VA-361	CR, KPC-2	4	>32	16
KI2	CR, NDM-1	8	>32	>32

Abbreviations: CR, carbapenem-resistant; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.
Figure adapted from Matsumoto et al. *Antimicrob Agents Chemother*. 2017.

K. pneumoniae) were observed in the rats recreating the human PK for cefiderocol 2 g q8h as a 1 h infusion

- In the rats recreating the simulated 3 h infusion, reductions ranged from 3.04 to 4.41 log_{10} CFU against all 5 CR isolates

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Pre-Clinical Studies (Cont.)

Table 4. Extrapolated $\%f_{T>MIC}$ Achieved with Human Exposure of Cefiderocol 2 g q8h as a 1 h or 3 h Infusion in Infected Rats[5]

Cefiderocol MIC (µg/mL)	$\%f_{T>MIC}$	
	1 h Infusion	3 h Infusion
0.125	100	100
0.25	100	100
0.5	100	100
1	100	100
2	100	100
4	75	100
8	50	100

Abbreviations: $\%f_{T>MIC}$, percentage of the dosing interval during which free-drug concentrations are above the MIC; g, gram(s); h, hour(s); MIC, minimum inhibitory concentration; q8h, every 8 hours.
Figure adapted from Matsumoto et al. *Antimicrob Agents Chemother*. 2017.

P. aeruginosa, *A. baumannii*, and *K. pneumoniae*) were observed in the rats recreating the human PK for cefiderocol 2 g q8h as a 1 h infusion

- In the rats recreating the simulated 3 h infusion, reductions ranged from 3.04 to 4.41 $\log_{10}$ CFU against all 5 CR isolates

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Pre-Clinical Studies (Cont.)

In vitro PD Model

Tsuji et al (2015) studied the bactericidal activity of cefiderocol against CRE, MDRP and MDRA in an *in vitro* PD model in which the drug concentration pattern closely resembled human PK. Cefiderocol MICs were determined by broth microdilution using ID-CAMHB.[6]

- The dose of cefiderocol was 2 g tid, given as 1 h and 3 h infusions
- Cefiderocol was evaluated against 8 MDR strains: 2 strains each of *P. aeruginosa*, *A. baumannii*, NDM-1-producing *E. coli*, and KPC-producing *K. pneumoniae*
- Table 5 shows MICs against the test strains. MDR strains were defined as having MICs of ≥16 µg/mL for imipenem, ≥32 µg/mL for amikacin, ≥4 µg/mL for ciprofloxacin, and ≥32 µg/mL for ceftazidime

Table 5. Test Strain Characteristics[6]

Test Strain	Characteristic	β-lactamase	Cefiderocol MIC (µg/mL)
E. coli DS474	CR strain		16
E. coli DU48916	CR strain		4
K. pneumoniae VA-384	CR strain		4
K. pneumoniae 8667	CR strain		2
P. aeruginosa SR27001	MDR strain		2
P. aeruginosa NUBL-7808	MDR strain		0.5
A. baumannii 8626	MDR strain	OXA-51	16
A. baumannii NCTC13424	CR strain, CC92	OXA-23, OXA-51 like	1

Results[6]

- For log_{10} reductions of viable bacterial counts for cefiderocol as 1 h and 3 h infusions, see Table 6. 1 h and 3 h infusions of cefiderocol 2 g tid demonstrated bactericidal activity (>3 log_{10} reduction) against all tested strains in this *in vitro* PD model

Table 6. Log_{10} Reduction of Viable Bacterial Count in an *In vitro* PD Model[6]

Test Strain	Log_{10} Reduction of Viable Bacterial Count from Initial Inoculum at 24 h	
	Cefiderocol 1 h Infusion	Cefiderocol 3 h Infusion
E. coli DU48916		–4.53*
E. coli DS474		<–4.64*
K. pneumoniae VA-384		<–4.66*
K. pneumoniae 8667		<–4.77*
P. aeruginosa SR27001		–3.30*
P. aeruginosa NUBL-7808		<–4.51*
A. baumannii NCTC13424		<–4.78*
A. baumannii 8626		<–4.38*

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Pre-Clinical Studies (Cont.)

Table 5. Test Strain Characteristics[6]

Test Strain	Characteristic	β-lactamase	Cefiderocol MIC (µg/mL)
E. coli DS474	CR strain	NDM-1	16
E. coli DU48916	CR strain	NDM-1	4
K. pneumoniae VA-384	CR strain	KPC, TEM-1, SHV	4
K. pneumoniae 8667	CR strain	KPC	2
P. aeruginosa SR27001	MDR strain	IMP-1	2
P. aeruginosa NUBL-7808	MDR strain	VIM-2	0.5
A. baumannii 8626	MDR strain	OXA-23, OXA-51	16
A. baumannii NCTC13424	CR strain, CC92	OXA-23, OXA-51 like	1

Abbreviations: CR, carbapenem-resistant; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MDR, multidrug-resistant; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; SHV, sulfhydryl-variable; TEM, Temoneira; VIM, Verona integron-encoded metallo-β-lactamase.
Figure adapted from Tsuji et al. IDWeek. 2015.

For log_{10} reductions of viable bacterial counts for cefiderocol as 1 h and 3 h infusions, see Table 6. 1 h and 3 h infusions of cefiderocol 2 g tid demonstrated bactericidal activity (>3 log_{10} reduction) against all tested strains in this *in vitro* PD model

Table 6. Log_{10} Reduction of Viable Bacterial Count in an *In vitro* PD Model[6]

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Pre-Clinical Studies (Cont.)

Table 6. Log_{10} **Reduction of Viable Bacterial Count in an *In vitro* PD Model**[6]

Test Strain	Log_{10} Reduction of Viable Bacterial Count from Initial Inoculum at 24 h	
	Cefiderocol 1 h Infusion	Cefiderocol 3 h Infusion
E. coli DU48916	<–4.83*	–4.53*
E. coli DS474	<–4.64*	<–4.64*
K. pneumoniae VA-384	<–4.66*	<–4.66*
K. pneumoniae 8667	<–4.77*	<–4.77*
P. aeruginosa SR27001	<–4.20*	–3.30*
P. aeruginosa NUBL-7808	<–4.51*	<–4.51*
A. baumannii NCTC13424	<–4.78*	<–4.78*
A. baumannii 8626	<–4.38*	<–4.38*

Abbreviation: h, hour(s).
*Bactericidal effect (>3 log_{10} reduction).
Figure adapted from Tsuji et al. IDWeek. 2015.

Fetroja® – Administration Less Than 3 Hours

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Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[7]

- 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:[7]

- Patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of **Fetroja**

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

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Abbreviations

AE	adverse event	MDR	multidrug-resistant
CFU	colony-forming unit	MDRA	multidrug-resistant *Acinetobacter* spp.
CLSI	Clinical and Laboratory Standards Institute	MDRP	multidrug-resistant *Pseudomonas aeruginosa*
COVID-19	coronavirus disease-19	MIC	minimum inhibitory concentration
CR	carbapenem-resistant	mITT	modified intention-to-treat
CrCl	creatinine clearance	NDM	New Delhi metallo-β-lactamase
CRE	carbapenem-resistant Enterobacterales	OXA	oxacillinase
CRKP	carbapenem-resistant *Klebsiella pneumoniae*	PD	pharmacodynamic
cUTI	complicated urinary tract infection	PK	pharmacokinetic
EA	early assessment	PTA	probability of target attainment
EOT	end of treatment	q8h	every 8 hours
FDA	US Food and Drug Administration	q12h	every 12 hours
FU	follow-up	RTI	respiratory tract infection
g	gram(s)	SAE	serious adverse event
GI	gastrointestinal	SHV	sulfhydryl variable
h	hour(s)	TEM	Temoneira
HABP	hospital-acquired bacterial pneumonia	tid	three times daily
ICU	intensive care unit	TOC	test of cure
ID-CAMHB	iron-depleted cation-adjusted Mueller Hinton broth	US	United States
IMP	imipenemase	VABP	ventilator-associated bacterial pneumonia
IV	intravenous	VIM	Verona integron-encoded metallo-β-lactamase
KPC	*Klebsiella pneumoniae* carbapenemase		

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Literature Search

As of February 2026, a computerized search of the published medical literature using internal and external databases (ie., Medline® and Embase®) has identified additional relevant references regarding cefiderocol administered less than 3 hours. For your review, these references are listed in the bibliography that follows:

Gatti M, Rinaldi M, Laici C, et al. Highly adsorptive removal of cefiderocol during continuous venovenous hemodiafiltration equipped with oXiris filter in an orthotopic liver transplant recipient having septic shock caused by VIM-producing *Klebsiella pneumoniae*. *Journal Antimicrob Chemother*. 2025;80(4):1153-1155. doi:10.1093/jac/dkaf040

Amadesi S, Gatti M, Rinaldi M, Pea F, Viale P, Gaibani P. Novel CMY-186 variant conferring cross-resistance to cefiderocol and ceftazidime/avibactam in *Klebsiella pneumoniae* from a critically ill patient during cefiderocol and ceftazidime/avibactam treatment. *Int J Antimicrob Agents*. 2024;63(4):107107. doi:10.1016/j.ijantimicag.2024.107107

Klein S, Boutin S, Kocer K, et al. Rapid development of cefiderocol resistance in carbapenem- resistant *Enterobacter cloacae* During therapy is associated with heterogeneous mutations in the catecholate siderophore receptor cirA. *Clin Infect Dis*. 2022;74(5):905-908. doi:10.1093/cid/ciab511

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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References

1. Portsmouth S, van Veenhuyzen 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. [Web Link]
2. Gastalver-Martín C, Serna-Romero O, Buendia-Bravo S, et al. Cefiderocol treatment in COVID-19 positive patients co-infected with pan-resistant *Pseudomonas aeruginosa*. *Eur J Hosp Pharm*. 2023;30(Suppl 1):A57. [Web Link]
3. Katsube T, Tenero D, Wajima T. S-649266 modeling and simulation for prediction of efficacy and dose optimization. Poster presented at: IDWeek 2014; October 8-12, 2014; Philadelphia, PA.
4. Tsuji M, Horiyama T, Nakamura R, et al. S-649266, a novel siderophore cephalosporin: efficacy against *Klebsiella pneumoniae* producing NDM-1 or KPC in rat lung infection model with recreated humanized exposure profile of 2 g dose with 1 or 3 h infusion. Poster presented at: IDWeek 2014; October 8-12; Philadelphia, PA.
5. Matsumoto S, Singley CM, Hoover J, et al. Efficacy of cefiderocol against carbapenem-resistant Gram-negative bacilli in immunocompetent-rat respiratory tract infection models recreating human plasma pharmacokinetics. *Antimicrob Agents Chemother*. 2017;61(9):e00700-17. [Web Link]
6. Tsuji M, Nakamura R, Kanazawa S, et al. S-649266, a novel siderophore cephalosporin: *in vitro* activities against multidrug-resistant and carbapenem-resistant Gram-negative pathogens in an *in vitro* pharmacodynamic model. Poster presented at: IDWeek 2015; October 7-11, 2015; San Diego, CA.
7. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

Enclosure

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