# Cefiderocol Sulfate Tosylate

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■ Cefiderocol sulfate tosylate is a siderophore cephalosporin antibiotic.

## USES

### ● *Respiratory Tract Infections*

#### Hospital-acquired and Ventilator-associated Bacterial Pneumonia

Cefiderocol sulfate tosylate is used for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

#### *Clinical Trials and Experience*

Efficacy and safety of cefiderocol for the treatment of HABP/VABP have been evaluated in a multicenter, randomized, double-blind, parallel-group, phase 3 noninferiority trial that included a total of 298 adults hospitalized with acute bacterial pneumonia (hospital-acquired pneumonia, ventilator-associated pneumonia, or healthcare-associated pneumonia) known or suspected to be caused by gram-negative bacteria (NCT03032380; trial 2). Patients were randomized 1:1 to receive cefiderocol (2 g every 8 hours given by IV infusion over 3 hours) or meropenem (2 g every 8 hours given by IV infusion over 3 hours) for 7–14 days; treatment could be extended to 21 days based on clinical assessment of the patient and dosage was adjusted if needed based on renal function. Patients in both treatment arms received open-label treatment with linezolid (600 mg every 12 hours for at least 5 day) for empiric coverage against gram-positive bacteria. The trial protocol permitted prior therapy with other active antibacterials if such therapy lasted no more than 24 hours within 72 hours prior to randomization; however, concomitant antibacterial therapy (systemic or via oral inhalation) was not permitted from the time of randomization until the test-of-cure (TOC) visit 7 days after the end of treatment; the protocol did not permit step-down to oral antiinfectives during the study. The primary efficacy end point was all-cause mortality at day 14 in the modified intention-to-treat (mITT) population, which included all randomized patients who received study drug and had evidence of bacterial pneumonia, except those with only anaerobic or gram-positive aerobic infections; secondary efficacy end points included all-cause mortality at day 28 and clinical cure (defined as resolution or substantial improvement in signs and symptoms associated with pneumonia, with no additional antibacterial treatment required for the current infection through the TOC visit). There were 292 patients in the mITT population (145 in the cefiderocol arm and 147 in the meropenem arm); the median acute physiology and chronic health evaluation II [APACHE II] score was 15 (29% had a baseline APACHE II score of 20 or greater), 68% were in an intensive care unit (60% were mechanically ventilated), and gram-negative bacteremia was present at baseline in 6% of patients. The baseline creatinine clearance was 80 mL/minute or less in 60% of patients (50 mL/minute or less in 34%, and less than 30 mL/minute in 14% of these patients); augmented renal clearance (creatinine clearance greater than 120 mL/minute) was present in 16% of patients. In both treatment groups, most patients (70%) received the study drug for 7–14 days and 18% received the study drug for 15–21 days.

Results indicated that cefiderocol was noninferior to meropenem based on the 14-day all-cause mortality rate in the m-ITT population in patients with HABP/VABP caused by gram-negative bacteria. (See Table 1.)

**TABLE 1. All-cause Mortality and Clinical Cure Rates at the TOC Visit in HABP/VABP Patients (m-ITT Population)**

| Study End Point | Cefiderocol | Meropenem |
|---|---|---|
| Day 14 all-cause mortality | 12.4% | 12.2% |
| Day 28 all-cause mortality | 22.1% | 21.1% |
| Clinical cure at TOC | 64.8% | 66.7% |

Results for cefiderocol and meropenem were stratified according to baseline lower respiratory pathogens that were susceptible to meropenem. (See Table 2 and Table 3.) Data for patients with infections caused by extended-spectrum β-lactamase (ESBL) producers (31% of patients in the cefiderocol arm and 28.6% of patients in the meropenem arm) indicate that all-cause mortality rates at days 14 and 28 were consistent with the overall results. Although there were 51 patients with *A. baumannii* complex at baseline, only 17 of these patients (33.3%) had isolates that were susceptible to meropenem. Results for all 51 patients with *A. baumannii* complex (regardless of susceptibility to meropenem) indicate that all-cause mortality at day 14, all-cause mortality at day 28, and clinical cure rate at the TOC visit were 19, 34.6, and 53.8%, respectively, in the cefiderocol arm compared with 16, 24, and 60%, respectively, in the meropenem arm.

**TABLE 2. All-cause Mortality Based on Baseline Pathogen Susceptible to Meropenem[a] in HABP/VABP Patients (mITT Population)**

| Baseline Pathogen | Day 14 All-cause Mortality: Cefiderocol | Day 14 All-cause Mortality: Meropenem | Day 28 All-cause Mortality: Cefiderocol | Day 28 All-cause Mortality: Meropenem |
|---|---|---|---|---|
| *K. pneumoniae* | 10.5% (4/28) | 11.1% (4/36) | 21.1% (8/38) | 25% (9/36) |
| *E. coli* | 16.7% (3/18) | 14.3% (3/21) | 27.8% (5/18) | 19% (4/21) |
| Other Enterobacterales[b] | 12.5% (2/16) | 14.3% (2/14) | 25% (4/16) | 21.4% (3/14) |
| *A. baumannii* complex[c] | 12.5% (1/8) | 0% (0/9) | 37.5% (3/8) | 0% (0/9) |
| *Ps. aeruginosa* | 10% (2/20) | 23.5% (4/17) | 10% (2/20) | 29.4% (5/17) |

[a] Susceptible defined as meropenem MIC 8 mcg/mL or less.

[b] Includes *E. cloacae* complex (*E. cloacae*, *E. asburiae*, *E. kobei*) and *S. marcescens*.

[c] Includes *A. baumannii*, *A. nosocomialis*, and *A. pittii*.

**TABLE 3. Clinical Cure Rate Based on Baseline Pathogen Susceptible to Meropenem[a] in HABP/VABP Patients (mITT Population)**

| Baseline Pathogen | Cefiderocol | Meropenem |
|---|---|---|
| *K. pneumoniae* | 63.2% (24/38) | 63.9% (24/36) |
| *E. coli* | 66.7% (12/18) | 61.9% (13/21) |
| Other Enterobacterales[b] | 62.5% (10/16) | 57.1% (8/14) |
| *A. baumannii* complex[c] | 75% (6/8) | 77.8% (7/9) |
| *Ps. aeruginosa* | 65% (13/20) | 76.5% (13/17) |

[a] Susceptible defined as meropenem MIC 8 mcg/mL or less.

[b] Includes *E. cloacae* complex (*E. cloacae*, *E. asburiae*, *E. kobei*) and *S. marcescens*.

[c] Includes *A. baumannii*, *A. nosocomialis*, and *A. pittii*.

### ● *Urinary Tract Infections*

#### Complicated Urinary Tract Infections

Cefiderocol sulfate tosylate is used for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, caused by susceptible *E. cloacae* complex, *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, and *Ps. aeruginosa*. The drug is one of several preferred options for the treatment of cUTIs caused by carbapenem-resistant Enterobacterales (CRE) and cUTIs caused by *Ps. aeruginosa* with difficult-to-treat (DTR) resistance.

#### *Clinical Trials and Experience*

Efficacy and safety of cefiderocol for the treatment of cUTIs, including pyelonephritis, were evaluated in a multinational, randomized, double-blind, parallel group phase 2 trial that included a total of 448 hospitalized adults (NCT02321800; trial 1). Patients were randomized 2:1 to receive cefiderocol (2 g every 8 hours given by IV infusion over 1 hour) or the fixed combination of

imipenem and cilastatin sodium (1 g of imipenem every 8 hours given as imipenem/cilastatin by IV infusion over 1 hour) for 7–14 days. The trial protocol did not permit a switch from IV to oral antibacterial therapy. Patients were excluded if baseline urine cultures indicated more than 2 uropathogens, fungal UTI, or uropathogens known to be carbapenem resistant. The primary efficacy end point was a composite of microbiologic eradication and clinical cure at the TOC visit in the microbiologic ITT (micro-ITT) population, which included all patients who received at least one dose of study drug and had at least one baseline gram-negative uropathogen. Other efficacy end points included the microbiologic eradication rate and the clinical response rate at TOC in the micro-ITT population. The micro-ITT population included 371 patients (252 in the cefiderocol arm and 119 in the imipenem/cilastatin arm); 25% had cUTI with pyelonephritis, 48% had cUTI without pyelonephritis, and 27% had acute uncomplicated pyelonephritis; complicating conditions included obstructive uropathy, catheterization, and renal stones; the most common baseline pathogens were *E. coli* and *K. pneumoniae*; and concomitant gram-negative bacteremia was identified in 7%. At baseline, creatinine clearance was greater than 50-80 mL/minute in 32%, 30-50 mL/minute in 17%, and less than 30 mL/minute in 3% of the micro-ITT population.

Results indicated that the composite end point of microbiologic eradication (defined as all gram-negative uropathogens found at baseline at concentrations of $10^5$ CFU/mL or greater reduced to less than $10^4$ CFU/mL) and clinical response (defined as resolution or improvement of cUTI symptoms and no new symptoms assessed by the investigator) at the TOC visit were greater in the cefiderocol arm compared with the imipenem/cilastatin arm. (See Table 4.) Although the microbiologic response at the TOC visit was greater with cefiderocol compared with imipenem/cilastatin, clinical response rates at the TOC visit were similar. Most patients who had microbiologic failure at the TOC visit in either treatment arm did not require further antibacterial treatment.

**TABLE 4. Composite, Microbiologic, and Clinical Response Rates at the TOC Visit in cUTI Patients (micro-ITT Population)**

| Study End Point | Cefiderocol | Imipenem/Cilastatin |
|---|---|---|
| Composite response | 72.6% | 54.6% |
| Microbiologic response | 73% | 56.3% |
| Clinical response | 89.7% | 87.4% |

When results for cefiderocol and imipenem/cilastatin were stratified according to baseline pathogens, results for the composite outcome at the TOC visit were consistent with those in the overall population. (See Table 5.) For bacterial isolates that were ESBL producers (24.2% of isolates in the cefiderocol arm and 26.9% of isolates in the imipenem/cilastatin arm), the composite response rate at the TOC visit also was consistent with the overall results.

**TABLE 5. Composite End Point of Microbiologic Eradication and Clinical Response Rates in cUTI Patients Based on Baseline Pathogen[a] (micro-ITT Population)**

| Baseline Pathogen | Cefiderocol | Imipenem/Cilastatin |
|---|---|---|
| *E. coli* | 74.3% (113/152) | 57% (45/79) |
| *K. pneumoniae* | 75% (36/48) | 48% (12/25) |
| *P. mirabilis* | 76.5% (13/17) | 0% (0/2) |
| *E. cloacae* complex | 61.5% (8/13) | 60% (3/5) |
| *Ps. aeruginosa* | 44.4% (8/18) | 100% (3/3) |

[a] Patients may have had more than one pathogen in the baseline culture.

Additional subgroup analyses examining outcomes by age, gender, and/or outcomes in patients with renal impairment, concomitant bacteremia, or acute uncomplicated pyelonephritis also indicated that results were consistent with those in the overall population.

## DOSAGE AND ADMINISTRATION

### ● *Administration*

Cefiderocol sulfate tosylate is administered by IV infusion.

Cefiderocol sulfate tosylate is commercially available as a white to off-white, sterile, lyophilized powder that must be reconstituted and diluted prior to IV infusion.

Although the drug is compatible with 0.9% sodium chloride injection and 5% dextrose injection, compatibility with other diluents or other drugs has not been established to date.

#### IV Infusion

##### *Reconstitution and Dilution*

The appropriate number of single-use vials labeled as containing 1 g of cefiderocol should be reconstituted by adding 10 mL of 0.9% sodium chloride injection or 5% dextrose injection to each vial. The vial(s) should be gently shaken to dissolve the powder and then allowed to stand until foaming disappears (typically takes no more than 2 minutes). The final volume in each reconstituted vial is approximately 11.2 mL. Reconstituted cefiderocol preferably should be immediately diluted by transferring to an appropriate IV infusion bag, but may be stored in the vial for up to 1 hour at room temperature.

To prepare the diluted solution, the appropriate volume of reconstituted cefiderocol should be transferred from the vial(s) into a 100-mL IV infusion bag containing 0.9% sodium chloride injection or 5% dextrose injection. (See Table 6.)

**TABLE 6. Instructions for Preparing Doses of Cefiderocol Using Reconstituted 1-g Vials of the Drug**

| Cefiderocol Dose | Required Number of Reconstituted 1-g Vials of Cefiderocol | Total Volume of Reconstituted Cefiderocol to be Transferred from Vial(s) into a 100-mL IV Infusion Bag |
|---|---|---|
| 2 g | 2 | 22.4 mL (11.2 mL [entire contents] from each vial) |
| 1.5 g | 2 | 16.8 mL (11.2 mL from first vial **and** 5.6 mL from second vial) |
| 1 g | 1 | 11.2 mL (entire contents of vial) |
| 0.75 g | 1 | 8.4 mL |

Reconstituted and diluted cefiderocol solutions should be inspected visually for particulate matter and discoloration prior to administration. The solution should appear clear and colorless and should not be used if it is discolored or contains particulates. Any vials containing unused reconstituted cefiderocol solution should be discarded.

The reconstituted and diluted cefiderocol solution is stable in the IV infusion bag for up to 6 hours at room temperature. Although the diluted solution may be stored for up to 24 hours in a refrigerator at 2–8°C protected from light; the IV infusion should be completed within 6 hours after removal from refrigeration.

##### *Rate of Administration*

IV infusions of cefiderocol should be given over 3 hours.

### ● *Dosage*

Dosage of cefiderocol sulfate tosylate is expressed in terms of cefiderocol.

#### Adult Dosage

##### *Hospital-acquired and Ventilator-associated Bacterial Pneumonia (HABP/VABP)*

For the treatment of HABP/VABP caused by susceptible gram-negative bacteria in adults, the recommended dosage of cefiderocol is 2 g IV every 8 hours in those with creatinine clearance of 60–119 mL/minute. In those with creatinine

clearance of 120 mL/minute or greater (e.g., seriously ill patients receiving IV fluid resuscitation), the recommended dosage is 2 g IV every 6 hours.

The recommended duration of cefiderocol treatment is 7–14 days; treatment duration should be guided by the clinical status of the patient.

#### *Complicated Urinary Tract Infections (cUTIs)*

For the treatment of cUTIs caused by susceptible gram-negative bacteria in adults, the recommended dosage of cefiderocol is 2 g IV every 8 hours in those with creatinine clearance of 60–119 mL/minute. In those with creatinine clearance of 120 mL/minute or greater (e.g., seriously ill patients receiving IV fluid resuscitation), the recommended dosage is 2 g IV every 6 hours.

The recommended duration of cefiderocol treatment is 7–14 days; treatment duration should be guided by the clinical status of the patient.

### ● *Special Populations*

#### Hepatic Impairment

Adjustment of cefiderocol dosage is not necessary in patients with hepatic impairment. (See Hepatic Impairment under Cautions.)

#### Renal Impairment

Cefiderocol dosage must be reduced in adults with creatinine clearance less than 60 mL/minute, including those receiving intermitted hemodialysis or continuous renal replacement therapy (CRRT). (See Table 7 and Table 8.)

In those with fluctuating renal function, regularly monitor creatinine clearance during treatment with the drug and adjust dosage as needed. (See Renal Impairment under Cautions.)

**TABLE 7. Recommended Cefiderocol Dosage in Adults with Creatinine Clearance less than 60 mL/minute**

| Estimated Creatinine Clearance[a] | Recommended Dosage |
|---|---|
| 30–59 mL/minute | 1.5 g every 8 hours |
| 15–29 mL/minute | 1 g every 8 hours |
| <15 mL/minute (with or without intermittent hemodialysis)[b] | 0.75 g every 12 hours |

[a] Creatinine clearance estimated by Cockcroft-Gault equation.

[b] Cefiderocol is removed by hemodialysis (60% of a dose removed by 3- to 4-hour hemodialysis session); administer initial dose immediately after a hemodialysis session.

### ● *Dosage in Patients Receiving Continuous Renal Replacement Therapy (CRRT)*

Dosage of cefiderocol in patients receiving CRRT, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) should be based on the CRRT effluent flow rate. The following dosage recommendations for such patients is intended to provide initial cefiderocol dosage; dosage may need to be adjusted based on residual renal function and the clinical status of the patient. (See Table 8).

**TABLE 8. Recommended Cefiderocol Dosage[a] in Adults with Creatinine Clearance less than 60 mL/minute Receiving CRRT**

| Effluent Flow Rate[b] | Recommended Dosage |
|---|---|
| ≤2 L/hr | 1.5 g every 12 hours |
| 2.1–3 L/hr | 2 g every 12 hours |
| 3.1–4 L/hr | 1.5 g every 8 hours |
| ≥4.1 L/hr | 2 g every 8 hours |

[a] Dosage recommendations for CRRT patients are intended to provide *initial* cefiderocol dosage; may need to adjust dosage based on residual renal function and clinical status of patient.

[b] Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.

#### Geriatric Patients

Dosage of cefiderocol should be selected with caution in geriatric patients. Dosage adjustments are not required based on age, but dosage should be adjusted based on renal function. (See Geriatric Use under Cautions.)

## CAUTIONS

### ● *Contraindications*

Cefiderocol sulfate tosylate is contraindicated in patients with known history of severe hypersensitivity to cefiderocol or other β-lactam antibacterials or other components of the preparation.

### ● *Warnings/Precautions*

#### Increased All-cause Mortality in Patients with Carbapenem-resistant Gram-negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with cefiderocol compared with 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 complicated UTIs (cUTIs) were included in the trial. BAT regimens varied according to local practices and consisted of 1–3 antibacterials with activity against gram-negative bacteria; most of the BAT regimens contained colistin (commercially available in the US as colistimethate sodium).

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 cefiderocol (24.8%) than in those treated with BAT (18.4%); all-cause mortality through day 49 remained higher in those treated with cefiderocol. Generally, deaths were in patients with infections caused by gram-negative bacteria, including non-fermenters such as *A. baumannii* complex, *Stenotrophomonas maltophilia*, and *Ps. 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.

Clinical response should be closely monitored in patients receiving cefiderocol for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) or cUTIs.

#### Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving β-lactam antibacterials. In clinical trials, hypersensitivity reactions were observed in some cefiderocol-treated patients. Such 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 experienced severe reactions when treated with cephalosporins.

Prior to initiation of cefiderocol therapy, patients should be queried about previous hypersensitivity reactions to cephalosporins, penicillins, or other β-lactam antibacterials.

Cefiderocol should be discontinued if an allergic reaction occurs.

#### Superinfection/Clostridioides difficile-associated Diarrhea

Use of cefiderocol may result in emergence and overgrowth of nonsusceptible organisms (e.g., *Candida*).

Treatment with anti-infectives alters normal colon flora and may permit overgrowth of *Clostridioides difficile* (formerly *Clostridium difficile*). *C. difficile* infection (CDI) and *C. difficile*-associated diarrhea and colitis (CDAD; also known as antibiotic-associated diarrhea and colitis or pseudomembranous colitis) have been reported with nearly all anti-infectives, including cefiderocol, and may range in severity from mild diarrhea to fatal colitis. *C. difficile* produces toxins A and B which contribute to development of CDAD; hypertoxin-producing strains of *C. difficile* are associated with increased morbidity and mortality since they may be refractory to anti-infectives and colectomy may be required.

CDAD should be considered in the differential diagnosis of patients who develop diarrhea during or after anti-infective therapy. Careful medical history is

necessary since CDAD has been reported to occur as late as 2 months or longer after anti-infective therapy is discontinued.

If CDAD is suspected or confirmed, antibacterial therapy not directed against *C. difficile* should be discontinued whenever possible. Patients should be managed with appropriate anti-infective therapy directed against *C. difficile* (e.g., fidaxomicin, vancomycin, metronidazole), supportive therapy (e.g., fluid and electrolyte management, protein supplementation), and surgical evaluation as clinically indicated.

### Seizures and Other CNS Adverse Reactions

Cephalosporins, including cefiderocol, 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 in patients with renal impairment.

Cefiderocol dosage should be based on creatinine clearance (see Dosage under Dosage and Administration). In patients with known seizure disorder, anticonvulsant therapy should be continued during cefiderocol therapy.

If CNS adverse reactions (including seizures) occur, patients should undergo a neurological evaluation to determine whether cefiderocol should be discontinued.

### Selection and Use of Anti-infectives

To reduce development of drug-resistant bacteria and maintain effectiveness of cefiderocol and other antibacterials, the drug should be used only for the treatment of infections proven or strongly suspected to be caused by susceptible bacteria.

When selecting or modifying anti-infective therapy, results of culture and in vitro susceptibility testing should be used. In the absence of such data, local epidemiology and susceptibility patterns should be considered when selecting anti-infectives for empiric therapy.

Information on test methods and quality control standards for in vitro susceptibility testing of antibacterial agents and specific interpretive criteria for such testing recognized by FDA is available at https://www.fda.gov/STIC. For most antibacterial agents, including cefiderocol, FDA recognizes the standards published by the Clinical and Laboratory Standards Institute (CLSI).

### Laboratory Test Interference

Cefiderocol may cause false-positive results in urine dipstick tests (e.g., urine protein, ketones, or occult blood). If positive results are reported for such dipstick tests, alternative clinical laboratory methods of testing should be used to confirm the results.

### Specific Populations

#### *Pregnancy*

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

Although available studies cannot definitively establish an absence of risk, published data from prospective cohort studies, case series, and case reports over several decades regarding use of cephalosporins in pregnant women have not identified an association between 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.

In developmental toxicity studies in rats and mice, there was no evidence of embryofetal toxicity, including drug-induced fetal malformations or reductions in fetal viability, when cefiderocol was administered during organogenesis at dosages providing mean AUCs 0.9 times (rats) or 1.3 times (mice) higher than the daily mean plasma exposure reported in patients with cUTIs receiving 2 g of cefiderocol by IV infusion every 8 hours. In a pre- and postnatal development study, cefiderocol was administered IV at doses up to 1 g/kg daily 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.

Cefiderocol crosses the placenta in pregnant rats (less than 0.5% of a dose detected in fetuses).

#### *Lactation*

It is not known whether cefiderocol distributes into human milk, affects breast-fed infants, or affects milk production.

Cefiderocol is distributed into milk in rats (peak concentrations in milk are reported to be approximately 6% of peak plasma concentrations).

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for cefiderocol and any potential adverse effects on the breast-fed child from cefiderocol or from the underlying maternal condition.

#### *Pediatric Use*

Safety and efficacy of cefiderocol have not been established in patients younger than 18 years of age.

#### *Geriatric Use*

Of the 148 patients with HABP/VABP who received cefiderocol in a clinical 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 reported in patients 65 years of age or older was similar to that reported in younger adults, and the incidence did not differ between those 65 years of age and older and those 75 years of age and older.

Of the 300 patients with cUTIs who received cefiderocol in a clinical 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 adults.

Cefiderocol is known to be substantially excreted by the kidneys, and the risk of adverse reactions to the 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 when selecting dosage and it may be useful to monitor renal function. Although dosage adjustments are not required based on age, dosage should be based on renal function. (See Renal Impairment under Dosage and Administration.)

#### *Hepatic Impairment*

Although the effects of hepatic impairment on the pharmacokinetics of cefiderocol have not been evaluated, hepatic impairment is not expected to alter cefiderocol elimination since hepatic metabolism/excretion represents a minor pathway of elimination for the drug.

#### *Renal Impairment*

Dosage adjustment of cefiderocol is required in patients with creatinine clearance less than 60 mL/minute, including those receiving hemodialysis.

Dosage adjustment of cefiderocol is required in patients receiving CRRT, including CVVH, CVVHD, and CVVHDF; dosage in such patients should be based on the effluent flow rate. (See Renal Impairment under Dosage.) Consider that residual renal function may change in patients receiving CRRT and improvements or reductions in residual renal function may warrant a change in cefiderocol dosage. A total of 16 patients receiving CRRT were included in cefiderocol clinical trials to date.

Renal function should be monitored regularly during cefiderocol therapy and dosage should be adjusted as needed.

### ● *Common Adverse Effects*

Patients with HABP/VABP: The most frequent adverse effects reported in 4% or more of patients treated with cefiderocol were elevated liver enzymes, hypokalemia, diarrhea, hypomagnesemia, and atrial fibrillation.

Patients with cUTIs: The most frequently reported adverse effects reported in 2% or more of patients treated with cefiderocol include diarrhea, infusion site reactions, constipation, rash, candidiasis (oral or vulvovaginal candidiasis, candiduria), cough, elevated liver enzymes, headache, hypokalemia, nausea, and vomiting.

## DRUG INTERACTIONS

In vitro, cefiderocol does not inhibit cytochrome P-450 (CYP) isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4. The drug is not an inducer of CYP1A2, 2B6, or 3A4 in vitro.

In vitro, cefiderocol is not an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump transporters, organic anion transporting polypeptide (OATP) 1B1, or multidrug and toxin extrusion (MATE) 1, and is not a substrate of P-gp, BCRP, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, MATE1, or MATE2-K.

Concomitant use of cefiderocol did not result in clinically important effects on the pharmacokinetics of furosemide (OAT1 and OAT3 substrate), metformin (OCT1, OCT2, and MATE2-K substrate), or rosuvastatin (OATP1B3 substrate).

### Antibacterials

There was no in vitro evidence of antagonism between cefiderocol and amikacin, the fixed combination of ceftazidime and avibactam (ceftazidime/avibactam), the fixed combination of ceftolozane sulfate and tazobactam sodium (ceftolozane/tazobactam), ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline, or vancomycin against Enterobacterales, *Ps. aeruginosa*, or *A. baumannii*.

Synergism between cefiderocol and some antibacterials (e.g., levofloxacin, polymyxin B, co-trimoxazole) against *S. maltophilia* has been demonstrated in vitro.

### β-Lactamase Inhibitors

In vitro studies indicate that combined use of cefiderocol and a β-lactamase inhibitor (e.g., avibactam, clavulanic acid, dipicolinic acid [not commercially available in the US]) results in lower MICs than use of the drug alone.

## DESCRIPTION

Cefiderocol sulfate tosylate is a siderophore cephalosporin antibacterial. The drug is a conjugate that contains a cephalosporin core with side chains similar to those in some other cephalosporins (cefepime, ceftazidime) and a catechol group that functions as an iron-chelating siderophore. This structure and the unique mechanism of action of cefiderocol results in enhanced stability against hydrolysis by many β-lactamases, including extended-spectrum β-lactamases (ESBLs) (e.g., TEM, SHV, CTX-M) and carbapenemases (e.g., KPC, NDM, VIM, IMP, OXA-23, OXA-48-like, OXA-51-like, OXA-58).

Cefiderocol is actively transported across the outer bacterial cell membrane into the periplasmic space by a siderophore iron uptake mechanism. In addition, passive diffusion of the drug into bacterial cells occurs via porin channels. After entry into the periplasmic space, cefiderocol dissociates from the iron and binds to penicillin-binding proteins (PBPs), primarily PBP3, and inhibits peptidoglycan synthesis. In vitro studies indicate that cefiderocol usually is bactericidal in action.

Following IV infusion of cefiderocol sulfate tosylate, peak plasma concentrations and AUC of cefiderocol increase proportionally with dose. Mean peak plasma concentrations of cefiderocol in patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) or complicated urinary tract infections (cUTIs) receiving 2 g of cefiderocol every 8 hours given by IV infusion over 3 hours (dosage adjusted based on renal function) were 111 or 115 mg/L, respectively. In patients with pneumonia requiring mechanical ventilation who received a 2-g dose by IV infusion over 3 hours (dose adjusted based on renal function) at steady state, cefiderocol concentrations in epithelial lining fluid ranged from 3.1–20.7 mg/L and 7.2–15.9 mg/L at the end of the IV infusion and at 2 hours after completion of the infusion, respectively. Cefiderocol is 40–60% bound to plasma proteins, primarily albumin. Cefiderocol is minimally metabolized (less than 10% of a dose). The drug is primarily excreted by the kidneys. After a single 1-g radiolabeled dose of cefiderocol given by IV infusion over 1 hour, 98.6% of total radioactivity was excreted in urine (90.6% as unchanged drug) and 2.8% was excreted in feces. The terminal elimination half-life of cefiderocol is 2–3 hours. The AUC of cefiderocol increases with decreasing renal function. In vitro data indicate that the effluent flow rate of CRRT is the major determinant of cefiderocol clearance. In patients receiving CRRT, dosage recommendations based on flow rate (see Renal Impairment under Dosage and Administration) are predicted to provide cefiderocol exposures similar to those observed when a dosage of 2 g every 8 hours is used in patients not receiving CRRT. Increased cefiderocol clearance has been observed in patients with creatinine clearances of 120 mL/minute or greater (e.g., seriously ill patients receiving IV fluids); increasing dosage to 2 g every 6 hours in such patients provides cefiderocol exposures comparable to those observed in patients with creatinine clearances of 90–119 mL/minute receiving a dosage of 2 g every 8 hours. Age (18–19 years of age), sex, and race do not have clinically important effects on the pharmacokinetics of the drug. The effect of hepatic impairment on the pharmacokinetics of cefiderocol has not been evaluated.

### Spectrum

Cefiderocol has a spectrum of activity that includes various gram-negative aerobic bacteria, including some multidrug-resistant gram-negative aerobic bacteria. Although cefiderocol has variable activity against some gram-positive bacteria and anaerobes in vitro, this activity is not considered clinically relevant.

Cefiderocol is active in vitro and in clinical infections (HABP/VABP, cUTIs) against *E. coli*, *E. cloacae* complex, *K. pneumoniae*, and *Ps. aeruginosa*. The drug also is active in vitro and in clinical infections (HABP/VABP) against *A. baumannii* complex and *S. marcescens* and is active in vitro and in clinical infections (cUTIs) caused by *P. mirabilis*.

Although cefiderocol is active in vitro against some other gram-negative aerobes, including *Achromobacter*, *Burkholderia cepacia* complex, *Citrobacter freundii* complex, *C. koseri*, *K. aerogenes*, *K. oxytoca*, *Morganella morganii*, *P. vulgaris*, *Providencia rettgeri*, and *Stenotrophomonas maltophilia*, the clinical importance of this in vitro activity is not known and efficacy for the treatment of infections caused by these bacteria has not been established in adequate and well-controlled clinical studies.

Cefiderocol has been active in vitro against some *S. maltophilia* isolates and a subset of isolates of Enterobacterales and *Ps. aeruginosa* resistant to other antibacterials (meropenem, fluoroquinolones, amikacin, cefepime, ceftazidime/avibactam, ceftolozane/tazobactam) and has been active in vitro against a subset of isolates of *A. baumannii* complex 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 resistance mechanisms: 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). The drug also demonstrated in vitro activity against a subgroup of *Ps. aeruginosa* genetically confirmed to contain VIM, IMP, GES, and AmpC; a subgroup of *A. baumannii* containing OXA-23, OXA-24/40, OXA-51, OXA-58, and AmpC; and a subgroup of *S. maltophilia* containing metallo-carbapenemase (L1) and serine β-lactamases.

In vitro, cefiderocol remained active against *K. pneumoniae* in the presence of porin channel deletions (OmpK35/36) and against *Ps. aeruginosa* in the presence of porin channel deletions (OprD) and efflux pump up-regulation (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY).

### Resistance

In vitro studies indicate that a combination of β-lactamases (including AmpC β-lactamase overproduction), modifications of PBPs, and mutations of transcriptional regulators that impact siderophore or efflux pump expression can result in increased cefiderocol MICs and may result in resistance to the drug in gram-negative bacteria.

*A. baumannii* with reduced in vitro susceptibility or resistance to cefiderocol has been reported. In one study, there was no clear relationship between cefiderocol resistance in *A. baumannii* and the presence of acquired β-lactamases (TEM-1, SHV-5 or SHV-12, or OXA-23) or with the expression of chromosomal β-lactamases.

Cefiderocol does not induce AmpC β-lactamase in *P. aeruginosa* or *E. cloacae*. Following in vitro exposure of gram-negative bacteria (including carbapenemase producers) to cefiderocol concentrations 10 times the MIC, the frequency of resistance development in these bacteria ranged from $10^{-6}$ to less than $10^{-8}$.

*E. cloacae* complex with AmpC-mediated resistance to ceftazidime/avibactam that also was resistant to cefepime and had reduced susceptibility to cefiderocol in vitro has been reported. Cross-resistance between cefiderocol and other antibacterial classes has not been reported to date.

## ADVICE TO PATIENTS

Advise patients that antibacterials, including cefiderocol, should only be used to treat bacterial infections and not used to treat viral infections (e.g., the common cold).

Importance of completing full course of therapy, even if feeling better after a few days.

Advise patients that skipping doses or not completing the full course of therapy may decrease effectiveness and increase the likelihood that bacteria will develop resistance and will not be treatable with cefiderocol or other antibacterials in the future.

Advise patients and their families that allergic reactions, including serious allergic reactions, could occur with cefiderocol and that serious reactions require immediate treatment. Ask patients about any previous hypersensitivity reactions to cefiderocol, other β-lactams (including cephalosporins), or other allergens.

Advise patients that diarrhea is a common problem caused by antibacterials. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. Importance of contacting a clinician if severe watery or bloody diarrhea develops.

Inform patients that cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when dosage was not reduced and in patients with a history of epilepsy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal supplements, as well as any concomitant illnesses.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

## PREPARATIONS

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Cefiderocol Sulfate Tosylate

| | | |
|---|---|---|
| **Parenteral** | | |
| **For Injection, for IV use** | 1 g (of cefiderocol) | **Fetroja®** Shionogi |

† Use is not currently included in the labeling approved by the US Food and Drug Administration.