Cefiderocol

Essential medicine status ✓

ATC codes: J01DI04

Indication	Carbapenem-resistant Pseudomonas aeruginosa ICD11 code: MG50.80
INN	Cefiderocol
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 1 g in vial (as sulfate tosylate) powder for injection
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Cefiderocol
DrugBank	Cefiderocol

Expert Committee recommendation

The Expert Committee noted that antimicrobial resistance is a global public health threat and that effective antibiotics against multidrug-resistant Gram-negative organisms, such as carbapenem-resistant Enterobacterales (a critical priority pathogen on WHO's priority pathogens list), are urgently needed. The Committee further noted that very few options are currently available to treat Gram-negative organisms that produce metallo-beta-lactamases, which are highly endemic in some WHO regions. Cefiderocol offers activity against some of the critical and high-priority multidrug-resistant, Gram-negative pathogens, including those producing metallo-beta-lactamases, against which other antibiotics listed on the EML have no or only limited activity. The Committee also accepted that cefiderocol has a safety profile consistent with other beta-lactams. The Expert Committee noted that the two double-blinded studies (APEKS-cUTI and APEKS-NP) on which regulatory authority approval of cefiderocol is based applied a non-inferiority design, a common practice in antibiotic trials. Both trials demonstrated that cefiderocol was non-inferior to carbapenems with regard to microbiological and clinical response and mortality, despite large non-inferiority margins being applied. Of note, the presence of an infection caused by multidrug-resistant organisms was not an inclusion criterion in these trials. In addition, the pathogen-focused phase III CREDIBLE-CR trial comparing cefiderocol with best available therapy showed similar clinical cure for treatment of infections caused by carbapenem-resistant Gram-negative bacteria. However, there was a higher mortality at the end of the study in the subset of patients infected with Acinetobacter spp. The Committee therefore recommended the inclusion of cefiderocol in the complementary list of the EML as a Reserve group antibiotic, based on an acceptable benefit-to-risk profile and high public health need. The increased mortality observed in the CREDIBLE-CR study was a major concern and deserves further, careful study. Therefore, the Expert Committee did not recommend cefiderocol for treatment of proven Acinetobacter spp. infections at this time. Given the nature of cefiderocol as a last-resort Reserve antibiotic, the Committee stressed that special attention should be given to antibiotic stewardship measures to avoid inappropriate use. Strategies and policies to ensure access to this high-cost antibiotic in low-resource settings also need to be defined.

Background

Cefiderocol has not been previously considered for inclusion on the EML, nor classified under the AWaRe (Access–Watch–Reserve) classification of antibiotics.

Public health relevance

Antimicrobial resistance is estimated to contribute to 700 000 deaths every year globally (1–3). If action is not taken, it is estimated that 10 million lives a year will be at risk from drug-resistant infections by 2050 (1). The WHO has identified carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Pseudomonas aeruginosa, and carbapenem-resistant, third-generation cephalosporin-resistant Enterobacteriaceae as critical priority pathogens against which new antibiotics are needed (4). Cefiderocol is a parenteral siderophore cephalosporin antibiotic with potent activity against a broad spectrum of Gram-negative pathogens, including these critical priority pathogens. In its 2018 surveillance report, the European Centre for Disease Prevention and Control reported an increase in resistance to currently available treatments across some Gram-negative pathogens between 2015 and 2018 (5). The European Centre estimates that about 700 000 infections and 33 000 deaths in the European Union and European Economic Area in 2015 were caused by from multidrug-resistant bacterial infections (2). Carbapenem resistance in P. aeruginosa, Klebsiella pneumoniae and Acinetobacter spp. contributed significantly to the number of estimated deaths (in total, about 9000 deaths). In 2015, in five countries (France, Germany, Italy, Spain and United Kingdom), the prevalence of carbapenem-resistant Gram-negative infections ranged between 0.14 per 100 000 in the United Kingdom and 3.05 per 100 000 in Italy (2). While carbapenemases appear to vary by geographical location, a recent surveillance study reports an overall increase in these enzymes (6,7). The prevalence of carbapenem resistance has been particularly high in Mediterranean countries, South America and Asia Pacific countries, except Japan (6,8).

Benefits

The applicant conducted a comprehensive and systematic literature review for cefiderocol, including in vitro and in vivo studies and any comparative or non-comparative studies and randomized clinical trials. In vitro studies The SIDERO-WT analysis investigated the activity of cefiderocol and relevant comparators against carbapenem-susceptible and carbapenem-resistant pathogens (9–11). To date, 30 459 samples have been tested, with 9205 Gram-negative clinical isolates tested in 2014–2015, 8954 in 2015–2016 and 10 470 in 2016–2017. Cefiderocol was effective at low minimum inhibitory concentrations (MICs) for more than 99% of isolates in each testing period. The latest surveillance SIDERO-WT study (2016–2017) showed that cefiderocol demonstrated activity against 99.4% of Gram-negative pathogens at a MIC of 4 microgram/mL compared with 90.2% for ceftazidime + avibactam, 84.3% for ceftolozane + tazobactam and 95.5% for colistin. In an analysis of difficult-to-treat resistant pathogens, cefiderocol demonstrated activity against 94.5% of difficult-to-treat resistant A. baumannii, 99.8% of P. aeruginosa and 98.3% of Enterobacterales; these pathogens were less susceptible to other available treatments. In addition, 98.7% of carbapenem-non-susceptible Enterobacteriaceae, and 96.4% of carbapenem-non-susceptible non-fermenters were sensitive cefiderocol at a MIC of ≤ 4 microgram/mL (12). The SIDERO-CR study collected carbapenem-resistant isolates and multidrug-resistant non-fermenter isolates from Europe, North America, South America and the Asia Pacific region (9,13). Cefiderocol showed potent in vitro activity against all of these pathogens, as well as activity against isolates with previously characterized resistance factors (13). In vivo studies APEKS-cUTI was a phase II, multicentre (multinational), double-blind, randomized, active-controlled, parallel-group non-inferiority study conducted in 452 hospitalized adults with complicated urinary tract infections, with or without pyelonephritis or acute uncomplicated pyelonephritis caused by Gram-negative pathogens (14). This study assessed the efficacy and safety of intravenous cefiderocol (2 g every 8 hours) compared with intravenous, high-dose imipenem + cilastatin (2 g every 8 hours). The primary efficacy endpoint was the composite of clinical outcome and microbiological outcome at test of cure. The response rate for the primary efficacy endpoint was 73% (183/252) in the cefiderocol group and 55% (65/119) in the comparator group. Cefiderocol met the criteria to demonstrate non-inferiority versus imipenem + cilastatin with a prespecified 20% margin. At follow-up, sustained clinical response was higher in the cefiderocol group than the comparator group (81.3% versus 72.3%), with an adjusted treatment difference of 9.02% (95% confidence interval (CI) –0.37% to 18.41%). The microbiological eradication rate in the modified intention-to-treat population was significantly higher at test of cure in the cefiderocol group than the comparator group (73.0% versus 56.3%). The adjusted treatment difference in favour of cefiderocol (17.25%, 95% CI 6.92% to 27.58%) was statistically significant. APEKS-NP was a multicentre, double-blind, randomized, phase III clinical study comparing cefiderocol with high-dose, extended-infusion meropenem for the treatment of hospital acquired bacterial pneumonia, ventilator-associated bacterial pneumonia or health care-associated bacterial pneumonia caused by Gram-negative pathogens (15). Of the 292 patients in the modified intention-to-treat population, 251 (86%) had a qualifying baseline Gram-negative pathogen, including 92 (32%) with K. pneumoniae, 48 (16%) with P. aeruginosa, 47 (16%) with A. baumannii and 41 (14%) with Escherichia coli. The all-cause mortality rate at day 14

was 12.4% for the cefiderocol group and 11.6% for the high-dose meropenem group (treatment difference 0.8%, 95% CI –6.7% to 8.2%, demonstrating the non-inferiority of cefiderocol, as the upper limit of the 95% CI was < 12.5%. For secondary endpoints of clinical cure and microbiological eradication at test of cure, results were similar between treatment groups. Clinical cure rates were 64.8% in the cefiderocol group and 66.7% in the high-dose meropenem group (treatment difference –1.8%, 95% CI –12.7% to 9.0%); microbiological eradication rates were 47.6% for cefiderocol group and 48.0% for high-dose meropenem group (treatment difference –0.8%, 95% CI –12.1% to 10.5%). The CREDIBLE-CR study was a small, randomized, open-label observational study to evaluate the efficacy of cefiderocol and best available therapy in patients with confirmed carbapenem-resistant infections (nosocomial pneumonia, bloodstream infections or sepsis, or complicated urinary tract infections) (16). No formal or inferential analyses were planned for any outcomes to detect differences between the treatment groups. Clinical and microbiological outcomes were similar between treatment groups overall, and by site of infection and causative carbapenem-resistant pathogen. The quality of the randomized studies was assessed by the applicants. The analysis concluded that the APEKS studies were of high quality with low risk of bias and the CREDIBLE-CR study was of moderate quality. Case reports of cefiderocol use for compassionate reasons and in expanded access programmes have also reported positive outcomes (17–25). A case series of cefiderocol treatment in COVID-19 and burn patients, all ventilated and with carbapenem-resistant infections of A. baumannii or other carbapenem-resistant Gram-negative bacteria reported a 90% survival rate after 30 days, with 70% of patients experiencing clinical success (26).

Harms

In total, across the APEKS-cUTI, APEKS-NP and CREDIBLE studies, 386 serious adverse events were reported: 226 in patients treated with cefiderocol, 103 in patients treated with meropenem, 17 in patients treated with imipenem + cilastatin and 40 in patients treated with best available therapy. In the total sample, 56/549 (10.2%) patients treated with cefiderocol experienced treatment-related adverse events and 45/347 (13.0%) patients using comparator treatments experienced treatment-related adverse events. Overall, there were fewer treatment-emergent adverse events with cefiderocol (344/549; 62.7%) than with comparator treatments (252/347; 72.6%). The most common adverse reactions for cefiderocol were diarrhoea (8.2%), constipation (4.6%), pyrexia (4.0%) and urinary tract infection (4.7%). In total, 22 serious adverse reactions were reported: eight in patients treated with cefiderocol, six in patients treated with meropenem, one in a patient treated with imipenem + cilastatin and seven in patients treated with best available therapy. The clinical safety for cefiderocol has been investigated in three randomized clinical trials, two specific to different infection sites and one specific to carbapenem-resistant pathogens. In total, 549 patients were treated with cefiderocol in these trails (14–16). In the APEKS-cUTI study, the proportion of patients who experienced at least one adverse event was lower in the cefiderocol group than in the imipenem + cilastatin group (41% versus 51%). The most common adverse events were diarrhoea (4% versus 6%), hypertension (4% versus 5%) and constipation (3% versus 4%), and there was an increased incidence of C. difficile colitis in the imipenem + cilastatin group compared with the cefiderocol group. Serious adverse events occurred in a smaller proportion of patients treated with cefiderocol than patients treated with imipenem + cilastatin (5% versus 8%) (14). In the APEX-NP study, overall, treatment-emergent adverse events and treatment-related adverse events were similar between treatment arms. Serious adverse events occurred in 36% of patients using cefiderocol and 30% of patients using meropenem. The most frequently observed adverse event was urinary tract infection (15.5% in the cefiderocol group and 10.7% in the meropenem group), hypokalaemia (10.8% cefiderocol group and 15.3% meropenem group) and anaemia (8.1% cefiderocol group and 8% meropenem group) (15). In the CREDIBLE-CR study, the cefiderocol group had a lower incidence of adverse events and treatment-related adverse events, but a higher incidence of death, serious adverse events and discontinuation due to adverse events, compared with the best available treatment group (16). The incidence of treatment-related adverse events leading to discontinuation was similar between treatment groups. More deaths occurred in the cefiderocol group than the best available treatment group. In an assessment by the investigator and two independent committees (one blinded), no deaths were found to be causally associated with cefiderocol. The mortality rate in the cefiderocol group was consistent with previous studies in similar populations with high levels of A. baumannii infections (27–29). However, the mortality rate in the best available treatment group was substantially lower than expected from previous studies (27–35). The reason for this lower than expected mortality is not clear. Still, it may be influenced by various factors related to baseline imbalances and other anomalies (such as the low mortality associated with high APACHE II and SOFA scores). Cefiderocol has demonstrated a manageable safety profile with the longest use being more than 90 days in a renal transplant patient where no apparent safety issues were observed (34).

Cost / cost effectiveness

Cefiderocol is appropriate for treating infections caused by aerobic Gram-negative organisms in adults who have limited treatment options. Treatment options may be limited because of multidrug-resistant or carbapenem-resistant pathogens, which are associated with higher mortality rates and increased clinical and economic burden. Without definitive evidence that an

infection is resistant to first-line treatment, empiric therapy may be used, and appropriate treatment may be delayed. A recent systematic review examined the effect of delayed antibiotic therapy in patients with severe bacterial infections. It concluded that mortality was significantly lower in patients who did not experience a delay in receiving the appropriate therapy (38). Several systematic reviews have examined the effect of antimicrobial resistance and multidrug-resistant infections on health care costs, and all found an association between increased costs and resistance (39–41). As a result, antibiotics that can effectively treat multidrug-resistant infections can potentially provide health benefits and health care savings. The wholesale acquisition of cefiderocol (10 vials) in the United Kingdom and the USA was reported in the application as £ 1319.00 and US$ 1833.33, respectively. Length of treatment varies from patient to patient, depending on infection site and underlying patient conditions. The dose of cefiderocol varies with renal function, but for a normal renal function, the standard dose is 2 g by infusion every 8 hours. This represents a daily dose of six vials a day, at a cost of £ 791.40 a day in the United Kingdom and US$ 1100 a day in the USA. A cost–effectiveness analysis compared cefiderocol with colistin-based regimens to treat complicated urinary tract infections and hospital-acquired and ventilator-associated pneumonia caused by confirmed carbapenem-resistant pathogens (42). It concluded that cefiderocol was a cost-effective option compared with the colistin-based treatment, with an incremental cost–effectiveness ratio of US$ 14 616 per quality-adjusted life year.

WHO guidelines

Cefiderocol is a newly approved antimicrobial so is not yet included in many formal clinical guidelines. However, its usefulness against several multidrug resistant pathogens has been recognized by both WHO and the Infectious Diseases Society of America (36,37). In the 2019 WHO report on antibacterial agents in clinical development, cefiderocol was identified as a siderophore cephalosporin that is active against many WHO priority pathogens, including extended spectrum beta-lactamase-producing Enterobacterales, K. pneumoniae carbapenemase and oxacillinase-48-producing Enterobacterales (36).

Availability

Cefiderocol is manufactured by Shionogi & Co. Ltd (Japan) and has regulatory approval from the US Food and Drug Administration and the European Medicines Agency. It is currently available in Germany, United Kingdom and USA. Reimbursement and health-technology assessments are in process in other European countries.

Other considerations

Comments on the application were received from the Department of Global Coordination and Partnership in the Division of Antimicrobial Resistance, which supported the inclusion of cefiderocol on the EML as a Reserve group antibiotic, particularly for use: in hospitalized patients with a confirmed or suspected carbapenem-resistant infection; or when cefiderocol is the best option based on pathogen susceptibility data; or when other treatment choices are inappropriate. The technical department highlighted the need for a mechanism and/or strategy to ensure access to and global affordability of cefiderocol, as well as the need for stewardship.

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