A.7	Cefiderocol

Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☐ No ☐ Not applicable Comments: The application request the inclusion of cefiderocol on the WHO Model List of Essential Medicines for the following reasons: • Antimicrobial resistance is a growing problem worldwide and patients need novel antibacterial options • Cefiderocol offers coverage of multidrug-resistant, gram-negative pathogens against which other listed antibiotics have no- or limited–activity • Cefiderocol has a safety profile consistent with other cephalosporins
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Cefiderocol has regulatory approval for use in patients 18 years of age or older who have limited or no alternative treatment options for the treatment of complicated urinary tract infections including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex. Its regulatory approval is based on limited clinical safety and efficacy data
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable The available data is very limited. Cefiderocol is commercially available in the UK, Germany and US. Prior to marketing, cefiderocol was studied in over 700 patients through clinical studies in what is obviously a limited number of subjects. In addition to experience in clinical trials and post-approval patient access, compassionate use programs have been in place since 2016. Approximately 300 requests for cefiderocol have been received through the compassionate use programs and 184 have been granted product. In the United States, the compassionate use program ended upon its becoming commercially available. However, in Europe, the Asia Pacific region and Canada (Special Access Programme) cefiderocol is still provided through compassionate use programs in for qualified patients who have limited treatment options and are not eligible for a clinical trial. The criteria for compassionate use of cefiderocol were highly restrictive and cefiderocol was used in patients with serious infections, most often due to CR non-fermenters, and with limited or no alternative options. The application includes the important relevant evidence acknowledging their strengths and limitations. The quality of the two randomized, controlled, double-blinded studies (**APEKS-cUTI** and **APEKS-NP**) and the randomized, open-label, non-inferential study (**CREDIBLE-CR**) was assessed to demonstrate the efficacy and safety profiles. Using the GRADE assessment system, the analysis concluded that the **APEKS** studies were of *high quality with low risk of bias* and the **CREDIBLE-CR** study was of *low quality with a high risk of bias.*

| Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication? | ☒ Yes
☐ No
☐ Not applicable
Within the limitations of the available data, three clinical studies are available - **APEKS-cUTI, APEKS-NP** and **CREDIBLE-CR**

APEKS-cUTI was a phase 2, multicenter, double-blind, parallel-group non-inferiority trial in adults ≥18 years of age admitted to hospital with a clinical diagnosis of complicated urinary tract infection (cUTI) with or without pyelonephritis or acute uncomplicated pyelonephritis. Patients were randomly assigned (2:1) to receive 1 h intravenous infusions of 2 grams of cefiderocol or 1 gram of each imipenem-cilastatin three times daily, every 8 h for 7–14 days. Patients were excluded if they had a baseline urine culture with more than two uropathogens, a fungal urinary tract infection, or pathogens known to be carbapenem resistant. The primary endpoint was the composite of clinical and microbiological outcomes 7 days after treatment cessation (test of cure). Non-inferiority margins of 15% and 20% for cefiderocol versus imipenem-cilastatin were decided. The primary efficacy analysis was done on a modified intention-to-treat population, which included all randomly assigned individuals who received at least one dose of study drug and had a qualifying Gram-negative uropathogen (≥1 × 10^5 colony-forming units [CFU]/mL). Safety was assessed in all randomly assigned individuals who received at least one dose of study drug, according to the treatment they received. 303 patients were randomly assigned to cefiderocol and 149 to imipenem-cilastatin. 252 patients in the cefiderocol group and 119 imipenem-cilastatin group had qualifying gram-negative uropathogen (≥1 × 10^5 CFU/mL) and were included in the primary efficacy analysis. At test of cure, the primary efficacy endpoint was achieved by 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem-cilastatin group, with an adjusted treatment difference of 18.58% (95%CI 8.23–28.92; p=0·0004), establishing the non-inferiority of cefiderocol. Cefiderocol was well tolerated. Adverse events occurred in 122/300 (41%) patients in the cefiderocol group and 76/148 (51%) patients in the imipenem-cilastatin group, with gastrointestinal disorders including diarrhea, constipation, nausea, vomiting, and abdominal pain the most common adverse events for both treatment groups (35 [12%] patients in the cefiderocol group and 27 [18%] patients in the imipenem-cilastatin group). The authors concluded Intravenous 2-gram infusions of cefiderocol three times daily was non-inferior compared with 1 gram of each of imipenem-cilastatin for the treatment of cUTI in people with multidrug-resistant gram-negative infections.

APEKS-NP was a randomized, double-blind, parallel-group, phase 3, non-inferiority trial that enrolled 18 years and older with hospital-acquired, ventilator-associated, or health-care-associated gram-negative pneumonia, and randomly assigned them to either 2 grams of cefiderocol or meropenem 2 g every 8 h for 7–14 days. All patients also received open-label intravenous linezolid (600 mg every 12 h) for at least 5 days. Participants were stratified at randomization by infection type and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤15 and ≥16). The primary endpoint was all-cause mortality at day 14 in the modified intention-to-treat (ITT) population defined as all patients receiving ≥1 dose of study drug, excluding patients with gram-positive monomicrobial infections. The analysis was done for all patients with known vital status. Non-inferiority was declared if the upper bound of the 95% CI for the treatment difference between cefiderocol and meropenem groups was less than 12.5%. Safety was investigated to the end of the study in the safety population, which included all patients who received at least one dose of study drug. 148 participants received cefiderocol and 152 meropenem. Of 292 patients in the modified ITT population, 251 (86%) had a qualifying baseline gram-negative pathogen, including *Klebsiella pneumoniae* (92 [32%]), *Pseudomonas aeruginosa* (48 [16%]), *Acinetobacter baumannii* (47 [16%]), and *Escherichia coli* (41 [14%]). 142 (49%) patients had an APACHE II score of 16 or more, 175 (60%) were mechanically |

ventilated, and 199 (68%) were in intensive care units at the time of randomization. All-cause mortality at day 14 was 18/145 (12.4%) with cefiderocol and 17/146 (11.6%) with meropenem adjusted treatment difference 0.8% (95%CI −6.6 to 8.2; p=0.002) for non-inferiority hypothesis). Treatment-emergent adverse events (TEAEs) were reported in 130/148 (88%) receiving cefiderocol and 129/150 (86%) receiving meropenem [UTI in 23/148 (16%) the cefiderocol group and hypokalaemia in 23/150 (15%) in the meropenem group]. The authors concluded cefiderocol was non-inferior to high-dose, extended-infusion meropenem in terms of all-cause mortality on day 14 in patients with gram-negative nosocomial pneumonia, with similar tolerability. The results suggest that cefiderocol is a potential option for the treatment of patients with nosocomial pneumonia, including those caused by multidrug-resistant gram-negative bacteria.

CREDIBLE-CR was a randomised, open-label, multicentre, parallel-group, pathogen-focused, descriptive, phase 3 study in patients 18 years or older admitted to hospital with nosocomial pneumonia, bloodstream infections or sepsis, or complicated urinary tract infections (cUTI), and evidence of a carbapenem-resistant gram-negative pathogen. Participants were randomly assigned (2:1) to receive either 2 grams of cefiderocol every 8 h or best available therapy (BAT, pre-specified by the investigator before randomization and comprised of a maximum of three drugs) for 7–14 days. For patients with pneumonia or bloodstream infection or sepsis, cefiderocol treatment could be combined with one adjunctive antibiotic (excluding polymyxins, cephalosporins, and carbapenems). The primary endpoint for patients with nosocomial pneumonia or bloodstream infection or sepsis was clinical cure at 7 ± 2 days after the end of treatment (test of cure) in the carbapenem-resistant microbiological with the intention-to-treat population as patients with a confirmed carbapenem-resistant gram-negative pathogen receiving at least one dose of study drug. For patients with cUTI, the primary endpoint was microbiological eradication at test of cure in the carbapenem-resistant microbiological ITT population. 101 patients received cefiderocol, and 51 best available therapy. 150 patients received treatment: 101 cefiderocol (85 [85%] received monotherapy) and 49 best available therapy (30 [61%] received combination therapy). In 118 patients in the carbapenem-resistant microbiological ITT population, the most frequent carbapenem-resistant pathogens were *Acinetobacter baumannii* (54 [46%]), *Klebsiella pneumoniae* (39 [33%]), and *Pseudomonas aeruginosa* (22 [19%]).

Efficacy		
	Cefiderocol group	**BAT group**
Infection	**Clinical cure**	**Clinical cure**
Nosocomial pneumonia	20/40 (50%, 95% CI 33.8–66.2)	10/19 (53%, 28.9–75.6)
Bloodstream infection or sepsis	10/23 (43%, 23.2–65.5)	6/14 (43%, 17.7–71.1)
	microbiological eradication	**microbiological eradication**
cUTIs	9/17 (53%, 27.8–77.0)	1/5 (20%, 0.5–71.6)
Safety		
TEAEs	92/101 (91%)	47/49 (96%)
Died by end of study	**34/101 (34%)**	**9/49 (18%)**

The authors concluded cefiderocol had similar clinical and microbiological efficacy to best available therapy in this heterogeneous patient population with infections caused by carbapenem-resistant gram-negative bacteria. **Importantly they noted numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp infections.** Collectively, they felt the findings from this study supports cefiderocol as an option for the treatment of carbapenem-resistant infections in patients with limited treatment options.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: In addition to less concerning potential adverse events, care should be exercised as follows: **All-cause mortality** - As noted, in **CREDIBLE-CR** there was an Increase in All-Cause Mortality in patients with carbapenem-resistant gram-negative bacterial infections were higher in patients treated with cefiderocol compared to those treated with best available therapy (BAT). Consequently, the United States FDA advises that one should reserve cefiderocol for use in patients who have limited or no alternative treatment options for the treatment of cUTI and that the clinical response to therapy in patients with cUTI be closely monitored **Hypersensitivity Reactions -** Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving betalactam antibacterial drugs. Hypersensitivity was observed with cefiderocol. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. Consequently, the United States FDA advises cefiderocol be discontinued if an allergic reaction occurs ***Clostridioides difficile*-Associated Diarrhea (CDAD) -** CDAD has been reported with nearly all systemic antibacterial agents, including cefiderocol and all patients should be evaluated with this in mind if diarrhea occurs. **Seizures and Other Central Nervous System (CNS) Adverse Reactions -** CNS adverse reactions such as seizures have been reported with cefedericol. Consequently, if focal tremors, myoclonus, or seizures occur, cefedericol should be discontinued.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments:As noted above, **All-cause mortality** - As noted, in **CREDIBLE-CR** there was an Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections: An increase in all-cause mortality was observed in cefiderocol-treated patients compared to those treated with best available therapy (BAT). Consequently, the United States FDA advises that one should reserve cefiderocol for use in patients who have limited or no alternative treatment options for the treatment of cUTI, and that the clinical response to therapy in patients with cUTI be closely monitored.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Acknowledging that (1) antimicrobial resistance is a growing problem worldwide and patients need novel antibacterial options and that (2) cefiderocol offers coverage of multidrug-resistant, gram-negative pathogens against which other listed antibiotics have no- or limited–activity – and recognizing that cefiderocol has a safety profile consistent with other cephalosporins leads to the conclusion that cefiderocol has an acceptable benefit to risk ratio. However, two things must be borne in mind. First the **APEKS** trials were non-inferiority trials, a common practice in antibiotic trials but even in this setting less than ideal. The non-inferiority margin for **APEKS-NP** was better than that for **APEKS-cUTI,** although the latter clearly exceeded its margin. Additionally, one cannot ignore the increase in all-cause mortality observed in **CREDIBLE-CR** in cefiderocol-treated patients compared to those treated with best available therapy (BAT). While this gives some pause it remains unexplained and was acknowledge by the United States FDA with the advice that cefiderocol be reserved for use in patients who have limited or no alternative treatment options for the treatment of cUTI and that the clinical response to therapy in patients with cUTI be closely monitored. It is expected that such will be its use worldwide.

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The available data is very limited. Cefiderocol is commercially available in the UK, Germany and US. Prior to marketing, cefiderocol was studied in over 700 patients through clinical studies in what was obviously a limited number of subjects. Given this, the highest priority should be given to the data from the published clinical trials that enrolled 552 of the 700 subjects for whom data is available, As noted above, the quality of the two randomized, controlled, double-blinded studies (**APEKS-cUTI** and **APEKS-NP**) and the randomized, open-label, non-inferential study (**CREDIBLE-CR**) was assessed to demonstrate the efficacy and safety profiles. Using the GRADE assessment system, the analysis concluded that the **APEKS** studies were of *high quality with low risk of bias* and the **CREDIBLE-CR** study was of *low quality with a high risk of bias.*
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: There are no special requirements that are not part of standard of care nor that would not be available where the proposed therapies would be administered.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Cost will undoubtedly be a major issue but one assumes an antibiotic such as this will be rigidly controlled by infectious disease specialists and this should limit their use to individuals with life-threatening infections at risk of dying who might benefit from such an antibiotic.
Any additional comments	None
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	As noted above, (1) antimicrobial resistance is a growing problem worldwide and patients need novel antibacterial options and that (2) cefiderocol offers coverage of multidrug-resistant, gram-negative pathogens against which other listed antibiotics have no- or limited–activity. The accumulated data, except for that in **CREDIBLE-CR** do not raise concerns regarding its safety, and the **CREDIBLE-CR** data remains unexplained and could very well be an outlier. One expects cost to be an issue and hopes infectious disease specialist will be the gatekeepers for containing costs and also the gatekeepers to help control the problem of resistance from worsening. One also hopes these specialists recognize the solid data speaks to non-inferiority not superiority providing support for very discretionary and restricted deployment of this novel antibiotic at their hospitals, recognizing existing options emerged comparably effective and in the case of **CREDIBLE-CR** possibly better tolerated. With these considerations in mind the cefiderocol submission should be considered for approval
References (if required)	