| A.7 | Cefiderocol – infections due to multi-drug resistant organisms |
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| Does the application adequately address the issue of the public health need for the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: |
| 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. | One of the few drugs that has activity against carbapenem resistant-Enterobacterales, Pseudomonas and Acinetobacter which are listed in critical category of WHO priority pathogen list. It has activity against NDM which is additional advantage. |
| Have all important studies and all relevant evidence been included in the application? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>If no, please provide brief comments on any relevant studies or evidence that have not been included: |
| Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).<br>**The APEKS-cUTI** study was a Phase 2, multinational, double-blind, randomized, active-controlled, parallel-group study conducted in hospitalized adult subjects with cUTIs caused by Gram-negative pathogens. At test of cure, clinical response was 89.7% (226/252) of patients in the cefiderocol group and 87.4% (104/119) of patients in the imipenem group. At follow up, sustained clinical response was higher in the cefiderocol group (81.3% [205/252] of patients) than in the IPM/CS group (72.3% [86/119] of patients), with an adjusted treatment difference of 9.02% (95% CI; -0.37%, 18.41%)<br>**The APEKS-NP** study was a multicenter, double-blind, randomized, phase 3 clinical study comparing cefiderocol with high-dose (HD), extended-infusion meropenem for the treatment of HABP, VABP or HCABP caused by Gram-negative pathogens. The all-cause mortality rate was 12.4% (18/145 subjects) for the cefiderocol group and 11.6% (17/146 subjects) for the high-dose (HD) meropenem group, demonstrating the noninferiority of cefiderocol, as the upper limit of the 95% CI was < 12.5% (95% CI: −6.6, 8.2). The secondary outcomes which included rates of microbiological eradication and clinical cure at test of cure were similar.<br>The CREDIBLE-CR study was a small, randomized, open-label study conducted to evaluate efficacy of cefiderocol for carbapenem resistant (CR) infections including nosocomial pneumonia, BSI/sepsis, or cUTI. The all cause mortality at the end of study in cefiderocol was 34% vs 9% in best available treatment control.<br>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? |

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| | Studies conducted only in adults and older adults. Pediatric studies are ongoing. Although studies included mainly high-income countries some low and middle-income countries were included. However no low- income country was included. |
| Does the application provide adequate evidence of the safety and adverse effects associated with the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: In the total sample, 56/549 (10.2%) patients treated with cefiderocol experienced treatment related AEs and 45/347 (13.0%) patients treated with comparators experienced treatment related AEs. Overall, there were less treatment emergent AEs with cefiderocol (344/549 [67.1%]) vs comparators (252/347 [72.6%]). The most common adverse reactions for cefiderocol were diarrhea (8.2%), constipation (4.6%), pyrexia (4.0%) and UTI (4.7%). |
| Are there any adverse effects of concern, or that may require special monitoring? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Patients with carbapenem resistant Acinetobacter infections should be carefully monitored due to increase mortality observed in this sub-group of patients. |
| Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.) | It is favourable. |
| Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.) | The quality of evidence is high for multi-drug resistant Gram-negative infections. However, for carbapenem resistant Gram-negatives the evidence is low due to small sample size. |
| Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?**<br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Should be only used in referral hospitals for targeted treatment of extremely drug resistant Gram-negative organisms where other therapeutic options are limited or not available. Patients with carbapenem resistant Acinetobacter infections should be carefully monitored due to increase mortality observed in this sub-group of patients. |
| Are you aware of any issues regarding the registration of the medicine by national regulatory authorities?<br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: Approved by US FDA and EMA |

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| 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<br>☒ No<br>☐ Not applicable<br>Comments: |
| Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings. | the dose of cefiderocol varies with renal function, but for a normal renal function, the standard dose is 2g on a 3h infusion, every 8h. This represents a daily dose of 6 vials a day, which is equivalent to:<br>- £ 791.4 per day in the UK<br>- $ 1,099.99 per day in the US<br><br>The cost is appropriate considering new drug but will be unaffordable in LMICs where burden of extremely drug resistant infections including those with NDM producing Gram-negative are highly prevalent |
| 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. | Cefiderocol should be included in EML and Reserve category of AWaRe. Patients with carbapenem resistant Acinetobacter infections should be carefully monitored due to increase mortality observed in this sub-group of patients.<br><br>One of the few drugs that has activity against carbapenem resistant-Enterobacterales, Pseudomonas and Acinetobacter which are listed in critical category of WHO priority pathogen list. It has activity against NDM which is additional advantage. The quality of evidence is high for multi-drug resistant Gram-negative infections. However, for carbapenem resistant Gram-negatives the evidence is low due to small sample size. |
| References (if required) | |