A.20	Imipenem + cilastatin + relebactam – bacterial infections due to multidrug-resistant organisms – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Imipenem/cilastin/relebactam (IMR) is a combination of a Group 2 carbapenem, a DHP-1 inhibitor, and a serine beta-lactamase inhibitor. IMR has an FDA label for cUTI, cIAI and HAP/VAP. IMR has broad activity against ESBLs and some carbapenemase producing Enterobacterales (mainly Class A carbapenemases - KPC and Class C – AmpC – but not Class B – MBLs and Class D - OXA). Although NDM and OXA are globally the most common genotypes associated with carbapemen resistance, KPC remains an important cause in some LMICs, where treatment options are limited. The RESTORE IMI 1 and 2 trials provided evidence that in patients with HAP/VAP, IMR had similar clinical activity to colistin/imipenem and piperacillin/tazobactam, with lower rates of renal toxicity to a colistin containing regimen. IMR is well tolerated and has a similar low toxicity profile to other commonly used beta-lactam antibiotics. IMR is a high-cost antibiotic.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: MDR gram negative serious bacterial infections are associated with a high mortality globally. Carbapenem resistant infections are a particular concern in LMIC settings, where polymyxins may be the only available treatment. The predominant genotypes in many LMIC settings are MBL or OXA, but in some LMIC's KPC genotype is an important cause of carbapenem resistance.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The RESTORE-IMI 1 trial randomised 31 patients with HAP/VAP/cIAI/cUTI to IMR and 16 patients to colistin+imipenem with a similar clinical response in both arms and lower rates of renal toxicity with IMR. RESTORE-IMI-2 was a Double Blind RCT of 537 patients with HAP/VAP comparing IMR to piperacillin/tazobactam (P/T). IMR demonstrated non-inferiority to P/T for all cause mortality and favourable clinical response with similar rates of AEs in both arms.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: IMR has a favourable safety profile, with similarly low rates of adverse events reported to other commonly used beta-lactam antibiotics.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: No AEs of concern specific to this agent.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: IMR is a high cost antibiotic. 2023 BNF prices are £3,800 for around one week of treatment. Health economic analyses are provided in the application of the cost effectiveness based on the willingness to pay thresholds in the US.
Are there 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: The application notes that IMR is currently registered in 28 countries.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: The 2022 WHO AWaRe Book notes that in developing guidance on the management of carbapenem resistant infections, because of the over reliance on observational data, the small clinical trial sample sizes and lack of comparative efficacy, toxicity, cost and selection of resistance between agents, no robust evidence based guidance can currently be provided.