A.9	Ceftolozane + tazobactam – bacterial infections due to multidrug-resistant organisms – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Ceftolazone/tazobactam (C/T) is a fixed dose combination of a fifth-generation cephalosporin antibiotic combined with a well-established beta-lactam inhibitor with particularly high activity against the WHO Priority Pathogen *Pseudomonas aeruginosa,* which is a common causative pathogen globally of hospital/ventilator acquired pneumonia (a major complication of severe/critical COVID-19). The ASPECT-NP study randomised 726 adults ventilated with nosocomial pneumonia in 263 hospitals in 34 countries to C/T or meropenem in a Phase 3 N/I trial. C/T was non-inferior to meropenem in terms of 28 day all-cause mortality or clinical test of cure (Kollef M LID 2019). C/T is well tolerated with no specific safety concerns. Many health economic evaluations have been performed in different HIC settings, for different clinical indications and with different comparator antibiotics. In general C/T drug costs are higher than the generic comparator antibiotics. Estimated additional benefit in terms of clinical outcomes provide a range of cost effectiveness estimates, depending on the threshold of willingness to pay/QALY.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Although the drug is licenced for use by the FDA and EMA for other indications (cUTI, c IAI), the key clinical indication for this application is for the treatment of HAP/VAP where multidrug resistant *Pseudomonas aeruginosa* infection is proven or suspected. In many ICU settings, high rates of AMR are commonly identified, with a carbapenem (eg meropenem) widely used as empiric therapy. C/T has activity against MDR *Pseudomonas aeruginosa* (PA) including Carbapenem Resistant PA (non-MBL).

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 ASPECT-NP study randomised 726 adults ventilated with nosocomial pneumonia in 263 hospitals in 34 countries to C/T or meropenem in a Phase 3 N/I trial. C/T was non-inferior to meropenem in terms of 28 day all-cause mortality or clinical test of cure (Kollef M LID 2019). Several observational studies have reported the efficacy of C/T in patients with MDR-PA (XDR and PDR). In general, similar efficacy, but lower rates of toxicity were reported in patients treated with C/T, compared to colistin/amikacin based regimens. Previous RCTs of C/T in cUTI and cIAI led to the licensing of C/T for these indications by the FDA and EMA.
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: The safety of C/T has been established in the ASPECT cUTI/cIAI/NP trials, demonstrating that the drug is well tolerated, with similar rates of AEs to the comparator agents used in these trials.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: There are no specific drug related AEs that are unexpected for this class of antibiotic or that require special monitoring. C/T has been studied in two paediatric studies in cUTI and cIAI, where the drug was well tolerated.
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: Observational data suggests that mortality is reduced if a rapid diagnosis of PA infection can be made in a patient with VAP and C/T treatment is started early. Rapid diagnostic tests for pathogen detection and genotypic resistance are now commercially available, focussing on the detection of Carbapenem Resistant PA (CRPA), which would help to identify whether C/T is likely to be of benefit.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Many health economic evaluations have been performed in different HIC settings, different clinical indications and with different comparator antibiotics. In general C/T drug costs are higher than the generic comparator antibiotics. Estimated additional benefit in terms of clinical outcomes provide a range of cost effectiveness estimates, depending on the threshold of willingness to pay/QALY. A key role for C/T is as a carbapenem sparing agent, in settings such as ICU's with high rates of patient colonisation with MDR pathogens. High carbapenem use in these settings is strongly associated with the emergence of resistance, but the health economic benefits of a carbapenem sparing strategy and the roles of specific drugs is complex.
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: C/T has been registered in 79 countries globally, including 25 LMICs.
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 application is to add C/T to the Reserve antibiotic list. The EML Antibiotic Working Group has recently published the AWaRe Book but noted that the evidence base for comparative clinical efficacy for Reserve antibiotics was insufficient at present to derive evidence based guidance on their appropriate use.