**Organisation name: NHS England and NHS Improvement**

**Disclosure:** I have no conflicts of interest or links to disclose

**Name of person completing form: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx**

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| 1 |  |  | NHSEI recognises the challenges of conducting a health technology assessment for antibiotics and that these assessments follow the multiple technology appraisal process. We believe that the use of high value clinical scenarios to estimate the patient level net health gains and then extrapolating to wider populations is a valid pragmatic approach.  We have one substantive comment on the method used in the report - it would benefit from a discussion of alternative resistance patterns. In particular, we would have liked to have seen a discussion of the ‘long tail’ scenario of a very low probability, but high impact event. This might be the state where resistance profiles to all other treatments has made those treatments ineffective against the relevant pathogens. We think this omission potentially neglects to address one of the main market failures that the payment model seeks to address – i.e. the long tail risk.  The report states ‘We did not model changes in resistance to existing AMs over time due to the sparsity of evidence available to inform these forecasts.’. We also note that the manufacturer did not model these changes in their assessment either. The important bit for NHSEI is not simply that the usage volume of the antimicrobial would increase, but that you would get a much higher incremental QALY gain for ceftazidime with avibactam in the absence of alternative treatments.  For example, if the incremental net health benefit per patient of ceftazidime with avibactam is 0.16 QALYs conditional on current alternative treatments being effective, this could increase to 7.8 - 9.0 QALY’s [if the hypothetical values apply from box 1, page 34] in the absence of effective alternatives – thus the value per patient increases by a factor of 50. If, for illustrative purposes, we assume a 1% chance of total resistance to existing alternative treatments occurring at some point over the 20 year period then the expected (probability weighted) net health benefit increase in terms of the QALYs per patient for the remaining period. As the treatment options will have diminished to just ceftazidime with avibactam, the population receiving this product would also need to be increased to the relevant treatment population. In this scenario as the remaining single treatment option the benefits are also likely to extend beyond the appraisal period of 20 years. |
| 2 |  |  | The empirical high-value clinical scenario would appear to offer the best INHBs, in contrast to microbiology-directed treatment. But the way the INHB are set out in the reports make it difficult for non-economists to understand the overall level of benefit. |
| 3 |  |  | Three patient characteristics were considered as relevant by clinical advisors in identifying patients are high risk of an MBL infection. Absent from this list is past exposure to carbapenem antibiotics. Was the clinical advisors’ opinion validated with published evidence of prognostic risk factors for MBL infection because there is certainly literature published on this subject? PICOS for high value clinical scenarios: CAZ-AVI section 3.2.3.1; cefidericol section 4.2.4. |
| 4 |  |  | From a clinical perspective, the fact that the model considers that a much broader population of patients would receive CAZ-AVI than considered appropriate by clinical advisors to EEPRU is welcomed because clinical experience in the past has demonstrated that many antimicrobials are used off-label, particularly for the treatment of difficult deep-seated infection, when susceptibility date indicate a limited range of treatment options |
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