NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Antimicrobial health technology evaluation

Draft guidance

Ceftazidime–avibactam for treating severe drug-resistant gram-negative bacterial infections

1 Conclusions

1.1 Ceftazidime–avibactam is recommended, within its marketing authorisation, as an option for treating severe drug-resistant infections caused by gram-negative bacteria. Following advice from specialists in microbiology or infectious disease, clinicians should offer ceftazidime–avibactam only if there are few alternative treatment options. This includes but is not limited to, infections caused by OXA-48 carbapenemase-producing *Enterobacterales*, and only if:

- microbiological susceptibility or gene testing has confirmed that the infection is susceptible to ceftazidime–avibactam or
- there is an urgent need to treat an infection expected to be susceptible to ceftazidime–avibactam and results of microbiological or gene tests are not yet available, and when there are few alternative treatment options.

Prescribers should follow the recommendations on new antimicrobials in the NICE guideline on antimicrobial stewardship.

1.2 The most plausible estimate of the value of ceftazidime–avibactam to the NHS in England over 20 years is approximately 8,880 quality-adjusted life years (QALYs) when the technology is used within its marketing authorisation and in line with the criteria in section 1.1.

Issue date: April 2022

1.3 The value of ceftazidime–avibactam assigned to each year of a 10-year contract between NHS England and the company should be at least 530 QALYs.

1.4 Because of the uncertainty in the estimates of the value of ceftazidime–avibactam to the NHS in England, NICE encourages research to further develop best practice in the health economic evaluation of antimicrobials (see sections 4 and 5).

1.5 This evaluation forms part of a project that develops and tests new models to evaluate and pay for antimicrobials. This draft guidance will inform commercial discussions between NHS England and NHS Improvement and the company that manufactures ceftazidime–avibactam. These discussions will seek to finalise a 3-year contract, with an option to extend the contract up to 10 years, during which the company will receive an annual payment based on the value of ceftazidime–avibactam to the NHS in England (see section 1.3). The payment will not be linked to the volume of ceftazidime–avibactam supplied.

2 Information about ceftazidime–avibactam

2.1 Ceftazidime–avibactam is a combination of ceftazidime, which is a third-generation cephalosporin, and avibactam, which is a next generation non-beta-lactam beta-lactamase inhibitor. Ceftazidime binds to a variety of bacterial penicillin-binding proteins, and avibactam inactivates a range of carbapenemase enzymes. Ceftazidime–avibactam is administered as an intravenous infusion over 2 hours, and given every 8 hours. Dosage adjustment is needed for people with renal impairment.

Marketing authorisation indication

2.2 Ceftazidime–avibactam (Zavicefta, Pfizer) is indicated in:

- adults and children aged 3 months and older for treating complicated intra-abdominal infection, complicated urinary tract infection including

pyelonephritis, and hospital-acquired pneumonia including ventilator-associated pneumonia

- adults with bacteraemia in association with, or that is suspected to be associated with, any of the infections listed above
- adults and children aged 3 months and older with infections caused by aerobic gram-negative organisms, when there are few treatment options.

Dosage in the marketing authorisation

2.3 The dosage schedule is available in ceftazidime–avibactam's summary of product characteristics.

3 Committee discussion

The antimicrobials evaluation committee considered the evidence submitted by Pfizer (the company that manufactures ceftazidime–avibactam) and other stakeholders, the assessment report from the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU), and consultation comments on EEPRU's report from stakeholders. See the committee papers for full details of the evidence.

Antimicrobial resistance and clinical need

Several mechanisms can lead to antimicrobial resistance

3.1 Antimicrobial resistance develops when bacteria that cause infection develop genetic mutations that make the antimicrobials less effective. Multi-drug-resistant bacteria can spread rapidly in hospitals and residential or care homes. This increases mortality and morbidity when infections can no longer be treated effectively, and when life-saving procedures such as chemotherapy or organ transplantation that rely on antimicrobials to prevent and treat infections cannot be done in people colonised with multi-drug-resistant bacteria. Although drugs in the carbapenem class historically have been reliably active against most common gram-negative bacterial infections, resistance to carbapenems is

now increasing. This results in fewer treatment options. Carbapenem resistance is classified based on whether or not the bacteria produce carbapenemase enzymes, which hydrolyse carbapenem antimicrobials, and make them ineffective. There are several treatments for infections with non-carbapenemase resistance mechanisms, but few treatment options for carbapenemase-mediated resistance. Carbapenemase enzymes are grouped into 2 main classes: serine carbapenemases and metallo-beta-lactamases. Ceftazidime–avibactam is active against serine carbapenemases, but not active against metallo-beta-lactamases. The main serine carbapenemases in the UK are *Klebsiella pneumoniae* carbapenemase and oxacillinases (in particular OXA-48). Many strains of *Enterobacterales* such as *Escherichia coli* and *K. pneumoniae* produce carbapenemases.

Multi-drug-resistant infections reflect an unmet need, and are a significant burden on patients and their families

3.2 The patient experts at the committee meeting explained that multi-drug-resistant infections are a potential ‘death sentence’, and people live with ‘feelings of fear and hopelessness’, knowing that they have few treatment options. They highlighted the negative impact that infections have on people’s psychological wellbeing because they may be hospitalised. Multi-drug-resistant infections negatively impact carers and families who may provide financial support. The patient experts explained that there was a high unmet need, particularly for people who are immunosuppressed and likely to develop severe multi-drug-resistant infections. They emphasised that the adverse effects of existing antimicrobials can significantly affect quality of life. The committee concluded that there was an unmet need, and patients and their families would welcome new effective treatments with reduced toxicity.

Antimicrobial resistance is a global challenge and there is an urgent need to invest in new antimicrobials

3.3 Antimicrobial resistance is a major global health challenge. New antimicrobials, especially those active against multi-drug-resistant pathogens, are subject to strict stewardship to slow the development of resistance. NICE defines stewardship as 'an organisational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness.' For many antimicrobials, there are few replacements or alternative products in development and even fewer that target multi-resistant pathogens. For many reasons, the pharmaceutical sector sees investment in novel antimicrobials as commercially unattractive. Companies cite as problems the high costs of research and development, post-marketing surveillance, and the logistics of maintaining supply chains. It is difficult for companies to recover these costs because of the strict stewardship, coupled with a limited period of market exclusivity, during which companies expect to generate most revenue. When generics enter the market at a lower price, this usually results in a substantial drop in sales of the original product. Sales of new antimicrobials may be low if there are few outbreaks of drug-resistant infections during the period of market exclusivity. New antimicrobials have failed in the market. In 2020, only 41 new antimicrobials were in phase 1 to 3 clinical trials, compared with some 1,800 immuno-oncology agents. The committee concluded that there is an urgent need to increase investment for new antimicrobials.

A new approach to 'delinked' reimbursement of antimicrobials involves estimating the population-level net benefit in quality-adjusted life years

3.4 In 2018, EEPRU published a framework for value assessment of new antimicrobials. In 2019, the UK agreed its 5-year action plan for antimicrobial resistance, in which it committed to testing a new way of reimbursing antimicrobials to incentivise research and development. The new reimbursement model will be a subscription-based contract, in which

the payments made by the NHS to the company manufacturing the antimicrobial do not depend on the volume of drugs supplied (also referred as 'delinked' payment). Instead, the payments will be based on the benefits that the antimicrobial offers to patients and to the NHS, which this NICE evaluation estimates. The subscription-based contract will last for 3 years, with an option to extend it up to 10 years. The committee's first objective was to estimate the incremental population net health benefits of ceftazidime–avibactam against the standard of care, as measured in quality-adjusted life years (QALYs) for the expected eligible population in England. This estimate was based on a model developed by EEPRU using a 20-year time horizon (see section 3.8), and additional evidence submitted by the company and other stakeholders. The committee's second objective was to decide what proportion of the total incremental population net health benefits NHS England should assign to the contract period.

Clinical evidence

The available clinical trials and observational studies have little relevance when evaluating ceftazidime–avibactam in multi-drug resistant infections

3.5 The 4 clinical trials identified by EEPRU's literature review for ceftazidime–avibactam were randomised non-inferiority trials done in people with infections susceptible to carbapenem antimicrobials. In addition, the trials were not done exclusively in the populations of interest for this evaluation and offered limited data on OXA-48 (the resistance mechanism of interest for this evaluation). The control treatments in the clinical trials were meropenem, doripenem, imipenem–cilastatin and best available therapy. EEPRU identified 6 observational studies but half of them were uncontrolled. Also, the studies had small sample sizes and included people with a range of different characteristics that likely would have affected their prognosis and how well their infections responded to treatment. The committee considered that the clinical trials and

observational studies had limited relevance when evaluating ceftazidime–avibactam in multi-drug-resistant infections.

Using data from in vitro susceptibility studies as a predictor of clinical outcomes is reasonable, but the results are uncertain

3.6 Because of the lack of relevant clinical trials or observational data, EEPRU assessed the relative clinical effectiveness of ceftazidime–avibactam using the laboratory-assessed susceptibility of a pathogen to antimicrobial treatment instead of using direct evidence on patient outcomes (see section 3.8 for the comparator treatments in EEPRU's model). This susceptibility is assessed in vitro, by culturing a bacterial sample from a patient along with increasing concentrations of the antimicrobial, to determine how well the antimicrobial slows growth. The clinical breakpoint for an isolate is a concentration threshold of the antimicrobial used to assess the likelihood of treatment success or failure. If the lowest concentration needed to stop bacterial growth is below the breakpoint, the infection is deemed susceptible, and treatment is likely to succeed. The committee was aware that different organisations use different laboratory methods to assess susceptibility and different methodologies to set clinical breakpoints. These organisations include the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI). EEPRU identified literature reporting a link between in vitro susceptibility data and clinical outcomes, but the evidence was not related to the pathogens and resistance mechanisms of interest. EEPRU used the results of 2 published studies identified in its literature review, which reported mortality and length of hospital stay conditional on susceptibility to treatment, to model clinical outcomes in the 'empiric treatment setting' of its model (see section 3.10). To model outcomes in the 'microbiology-directed treatment setting', EEPRU elicited information from experts using established methods to characterise the relationship between susceptibility data and clinical outcomes. Results were available from between 5 and 7 experts, depending on the question. These outcomes included mortality, length of

hospital stay, and type of hospital ward. EEPRU assumed that outcomes were conditional only upon a pathogen's in vitro susceptibility to the antimicrobial, and outcomes were the same regardless of the resistance mechanism causing the infection. Consultation comments on EEPRU's report highlighted that these assumptions were not plausible and introduced uncertainty into the modelling. Consultees commented that in vitro data would not account for clinical factors affecting response to treatment (for example, antimicrobial tissue penetration differs by infection sites). The clinical experts confirmed that there are other factors that affect treatment efficacy and outcomes. The consultees highlighted the small sample size of the expert elicitation. The clinical experts attending the committee meeting explained that, in the absence of alternative evidence and better estimates, using susceptibility as a predictor for clinical outcomes in EEPRU's model was reasonable. The committee concluded that susceptibility was a reasonable proxy for clinical outcomes but recognised that it introduced uncertainty in the model.

EEPRU's base-case economic model included the most appropriate susceptibility studies

3.7 EEPRU compared pathogen susceptibility to ceftazidime–avibactam with susceptibility to other antimicrobials. It used a network-meta-analysis that combined data from susceptibility studies identified through a systematic literature review and hospital laboratory data provided by the UK Health Security Agency (UKHSA; formerly Public Health England [PHE]). The studies reported the proportion of samples that were susceptible to ceftazidime–avibactam and the comparators. The laboratory methods and breakpoints used to assess susceptibility differed between studies. EEPRU therefore chose to group data in different networks because they were not directly comparable. In its base-case economic model, EEPRU used a network meta-analysis of studies that applied the EUCAST laboratory methods and breakpoints, supplemented by the data provided by the UKHSA. EEPRU chose this approach because it considered EUCAST methods and breakpoints to be the most applicable to England,

because the British Society for Antimicrobial Chemotherapy recommends that EUCAST methods and breakpoints should be used in clinical practice. EEPRU assumed that data reported to the UKHSA used EUCAST methods, because it was collected in the UK. Consultation comments on EEPRU's report noted that EUCAST and CLSI laboratory methods and breakpoints had recently been standardised and CLSI laboratory methods and breakpoints were an acceptable alternative to EUCAST. One consultee cautioned that EUCAST breakpoints should not be applied to data generated by CLSI laboratory methods, and vice versa, although another consultee disagreed. EEPRU did 3 scenario network meta-analyses to test the impact of using different studies. One scenario used all the studies regardless of whether they used EUCAST or CLSI laboratory methods or breakpoints. Another used only the UKHSA susceptibility data. The final scenario used the only study that focused solely on the resistance mechanism of interest, OXA-48 (that is, the study excluded pathogens with co-existing OXA-48 and metallo-beta-lactamase resistance mechanisms), and also used EUCAST methods. The other susceptibility studies in the EUCAST network, and the UKHSA data, did not explicitly exclude pathogens with co-existing metallo-beta-lactamases. EEPRU explained the limitations of the scenario analyses. The committee heard that it might not be appropriate to combine data based on EUCAST breakpoints and laboratory methods with data based on CLSI breakpoints and laboratory methods. It preferred the base-case network meta-analysis to the first scenario. The committee agreed that the second scenario was inappropriate because the UKHSA data was not generalisable to England. This was because susceptibility test results have not always been routinely submitted to UKHSA, and some relevant comparators were missing. The committee felt that the final scenario was inappropriate because the results seemed clinically implausible (the estimated odds ratio for being susceptible to ceftazidime–avibactam compared with colistin was substantially higher than in the other scenarios) and were unlikely to be generalisable to England. This is because the study was

done in Spain, which has different rates and mechanisms of carbapenemase-mediated resistance. The committee concluded that the network meta-analysis EEPRU used in its base case economic model was an appropriate source of susceptibility evidence.

Economic evidence

The comparator treatments in EEPRU's model are appropriate

3.8 Current standard care for treating infections suspected or confirmed to be caused by OXA-48-producing *Enterobacterales* includes a range of antimicrobials. Treatment choice depends on the infection site, whether the pathogen and resistance mechanism has been confirmed by microbiology testing, and whether the pathogen has additional mechanisms of resistance. EEPRU included a range of comparators, such as meropenem with colistin; fluoroquinolones with meropenem; aminoglycosides; cephalosporins; aztreonam with fosfomycin or colistin; tigecycline with meropenem, colistin or both; and other combinations. When more than one formulation was available, EEPRU assumed all comparators were given intravenously. The clinical experts explained that treatment is usually a combination of 2 or 3 agents, and confirmed that EEPRU's comparators were appropriate. To simplify its approach to modelling, EEPRU classified patients into 2 groups. These were people with an infection:

- susceptible to colistin-based therapy or aminoglycoside-based therapy
- not susceptible to colistin-based therapy or aminoglycoside-based therapy.

The clinical experts agreed that it was appropriate to consider colistin and aminoglycosides separately from other antimicrobials because they are associated with a higher risk of renal toxicity, which is higher with colistin than aminoglycosides. The clinical experts also explained that a proportion of people at risk of severe and potentially irreversible renal damage would not be offered colistin or aminoglycosides in practice, even

if no other effective antimicrobials were available (see section 3.16). The committee concluded that the comparators and classification of comparators in EEPRU's analyses were appropriate.

EEPRU modelled benefits of ceftazidime–avibactam in 2 stages: at the individual patient level and at the population level

3.9 EEPRU quantified the benefits of ceftazidime–avibactam in 2 stages. First, it developed a new decision analytic model to estimate the costs and benefits of ceftazidime–avibactam over a patient's lifetime (the 'patient-level model'). It modelled the clinical effectiveness, safety, quality of life, costs and resource use associated with ceftazidime–avibactam and its comparators. To inform a 'value-based' delinked payment contract between NHS England and the company, the output of the model is incremental net health benefit, expressed in QALYs at a population level. This differs from NICE's usual approach in health technology assessment of estimating the incremental cost-effectiveness ratio (ICER) at a patient level. EEPRU set the price of the drug to zero, and modelled costs of ceftazidime–avibactam related only to the use of healthcare resources. To convert any cost savings (or losses) associated with ceftazidime–avibactam (for example, reduced or increased time spent in hospital) into health benefits measured in QALYs, EEPRU used an estimate of health opportunity cost. As per the NICE scope for this evaluation, EEPRU used £20,000 per QALY as the estimate of health opportunity cost. This means that for every £20,000 saved, 1 QALY of health can be generated in the NHS. In the second stage, after estimating the per-patient benefits of ceftazidime–avibactam, EEPRU then considered the size of the population currently eligible for treatment and how this would change over time to account for a growing number of people with infections and emerging resistance to ceftazidime–avibactam and other antimicrobials. EEPRU modelled the benefits of ceftazidime–avibactam over a 20-year time horizon. This allowed EEPRU to estimate the long-term costs and benefits of ceftazidime–avibactam at the population level.

The modelled population is smaller than the population that would be offered ceftazidime–avibactam in practice

3.10 The marketing authorisation of ceftazidime–avibactam is broad. EEPRU's analysis was narrower than the marketing authorisation and focused on populations for whom it expected ceftazidime–avibactam to have the greatest clinical benefit, referred to as 'high-value clinical scenarios'. EEPRU divided the clinical scenarios into 2 treatment settings: 'empiric' and 'microbiology-directed'. The first, 'empiric', reflects clinically urgent infections requiring 'empiric' treatment, when clinicians strongly suspect a particular resistant organism and its mechanism of resistance. EEPRU defined the empiric treatment setting as fulfilling one of the following criteria: a person previously admitted to a hospital with a high prevalence of the suspected pathogen, a ward outbreak, or cultures taken during the current or previous hospital stay showing the person had an infection or bacterial colonisation. The second scenario was 'microbiology directed' and referred to the organism having been identified, and the microbiological susceptibility of the pathogen having been tested and confirmed. EEPRU included several high-value clinical scenarios in its patient-level analyses: hospital-acquired pneumonia and ventilator-associated pneumonia treated empirically; and complicated urinary tract infection, hospital-acquired pneumonia and ventilator-associated pneumonia in the microbiology-directed setting. EEPRU focused on infections with *Enterobacterales* with OXA-48 mechanisms of resistance. In its population-level model, EEPRU included additional groups of patients in whom ceftazidime–avibactam is expected to have clinical benefit and be used in practice: people with bloodstream and intrabdominal infections. Consultation comments on EEPRU's report suggested that ceftazidime–avibactam is effective against, and would be used to treat, pathogens and resistance mechanisms that EEPRU had not included in either its patient- or population-level analysis. For example, serine carbapenemase-producing *Pseudomonas aeruginosa* against which other treatment options are not available or appropriate. Consultees

highlighted the importance of ceftazidime–avibactam for people with compromised immune systems (for example, pre- or post-transplantation, or during cancer treatment), and other scenarios including but not limited to renal complications, cystic fibrosis, and burns. The committee agreed that EEPRU's analysis excluded populations that would benefit from ceftazidime–avibactam. EEPRU's estimates of the number of people eligible for ceftazidime–avibactam ranged between 300 and 500 people per year in England, while the company estimated that 1,400 people in the UK receive ceftazidime–avibactam per year. The committee was aware that its guidance applies only to England. A committee member with specialist expertise in infectious disease noted that recent data from NHS England and NHS Improvement suggests that approximately 1,200 people per year in England receive ceftazidime–avibactam. The committee noted that current usage of ceftazidime–avibactam was limited and guided by principles of good antimicrobial stewardship, so agreed that the annual estimates are likely to reflect appropriate use. The committee concluded that the current population size is likely to be approximately 2 to 3 times bigger than EEPRU's estimate.

It is reasonable to generalise incremental benefits of ceftazidime–avibactam to a wider population using results from the high-value clinical scenarios

3.11 When modelling benefits of ceftazidime–avibactam at the population level, EEPRU included additional infection sites where it expected ceftazidime–avibactam would be used and would provide benefit, notably, bloodstream and intrabdominal infections. Because EEPRU did not include these infection sites in its patient-level model, it was unable to estimate the patient-level QALY gains for these populations. EEPRU assumed that QALY gains in people with bloodstream infections were the same as those in people with hospital-acquired pneumonia and ventilator-associated pneumonia. EEPRU further assumed that QALYs gains in people with intra-abdominal infections were the same as those in people

with complicated urinary tract infections. The committee noted there was no evidence to show that QALY gains would differ between high-value clinical scenarios and these other infection sites in a wider-use population. In the absence of evidence to suggest otherwise, the committee recognised that EEPRU's assumptions introduced further uncertainty in the model, but concluded that it is reasonable to generalise incremental benefits of ceftazidime–avibactam to a wider population using results from the high-value clinical scenarios.

The clinical advisers' classification of infection site should be used to estimate the number of people eligible for ceftazidime–avibactam

3.12 EEPRU estimated the number of people currently eligible for ceftazidime–avibactam using data from the UKHSA Second Generation Surveillance System (SGSS), a national database of microbiology test results from 98% of hospital laboratories in England. It includes information on the mechanism of resistance and susceptibility to different antimicrobials for each isolate tested and submitted. It does not include direct information on the site of infection, which must be inferred from the specimen type submitted so is uncertain, as confirmed by the clinical experts at the committee meeting. The clinical experts explained that the UKHSA SGSS data represents isolates classified as susceptible to ceftazidime–avibactam through laboratory testing, rather than infections treated by ceftazidime–avibactam in practice. Therefore, the UKHSA SGSS data may overestimate the eligible population because it includes isolates that may not cause significant clinical illness needing an antimicrobial. The UKHSA SGSS data might also underestimate the eligible population because not all hospitals have a microbiology laboratory, and the data submitted to the SGSS from other hospitals may be incomplete. The clinical experts did not know whether the overall effect of these factors resulted in EEPRU overestimating or underestimating the eligible population size. EEPRU explored 2 ways of establishing the infection site from the SGSS data: 1 based on the UKHSA's classification of the specimens and 1 based on classification by EEPRU's clinical advisers.

EEPRU's clinical advisers considered that the UKHSA's classification system would underestimate the number of people eligible for ceftazidime–avibactam, because it excluded several specimen types. For example, the UKHSA's classification excluded sputum samples from estimates of pneumonia and excluded urine specimens from women from estimates of complicated urinary tract infections. The committee noted that EEPRU estimated an eligible population size of 300 people when using the UKHSA's classification, and 500 people when using the clinical advisers' classification. On balance, while acknowledging uncertainty, the committee concluded that it preferred the clinical advisers' infection site classification.

The number of people with OXA-48-producing *Enterobacterales* infections is likely to continue increasing in the long term

3.13 To forecast how the population eligible for ceftazidime–avibactam might change over the 20-year modelled time horizon, EEPRU used historical data on population size for people infected with the pathogen and resistance mechanism of OXA-48-producing *Enterobacterales*, provided by the Antimicrobial Resistance and Healthcare Associated Infections national reference laboratory. EEPRU excluded data from before October 2012 because of small patient numbers, and excluded data from after March 2018 because of an anomalous decrease in reporting caused by changes in guidelines. EEPRU applied 2 alternative methods to extrapolate data to forecast growth in the patient population: a 'persistent growth' model in which the growth persists over time, and a 'damped trend' model in which the population grows in the short term and stabilises in the long term. The committee appreciated that the choice of model had a significant effect on the long-term estimates. EEPRU provided base-case economic analyses including both approaches. The committee recognised that there was little evidence to support one over the other, and there was considerable uncertainty in both. However, the committee noted that the persistent growth model best fitted the data and was more clinically plausible. The committee concluded that it was more appropriate

to assume that the population size of people with OXA-48-producing *Enterobacterales* infections would continue to grow over the modelled time horizon rather than stabilise.

Resistance to ceftazidime–avibactam is expected to increase by approximately 5% over the next 20 years

3.14 Based on evidence that resistance develops to a new antimicrobial as its usage increases, EEPRU assumed that resistance to ceftazidime–avibactam would also increase over the model's 20-year time horizon. EEPRU used data from the European Antimicrobial Resistance Surveillance Network to model the relationship between antimicrobial use and resistance, which predicted a small increase in resistance of 0.03% over 20 years. EEPRU considered this value underestimated true resistance and explored 4 alternative assumptions in its base-case model: resistance to ceftazidime–avibactam reaching 1%, 5%, 10% or 30% after 20 years. EEPRU and the company agreed that 30% was an extreme estimate. The company noted that current resistance to ceftazidime–avibactam is not mediated by OXA-48 carbapenemases, but other carbapenemases. The clinical experts explained that it is not unusual to see a 20% increase in resistance to antimicrobials over a 20-year period. They explained that indiscriminate use of ceftazidime–avibactam would result in at least a 10% increase in resistance over the 20-year modelled time horizon, but if principles of good antimicrobial stewardship were followed then the increase in resistance would be between 3% and 5%. The committee concluded that it was reasonable to assume a 5% increase in resistance to ceftazidime–avibactam over the 20-year modelled time horizon.

The model should account for increased resistance to comparators over time, but there is uncertainty in the estimates of resistance

3.15 In its base-case model, EEPRU assumed that resistance to the comparators remains constant over time, because it found little evidence to inform extrapolations of current resistance rates. However, EEPRU

acknowledged that resistance to comparators would likely increase over time, either because new multi-drug-resistant pathogens would emerge, or because currently susceptible pathogens would become resistant to existing drugs. This would increase the incremental benefits of ceftazidime–avibactam. The committee noted that in modelling the emergence of resistance to existing antimicrobials, it was important to account for the benefits of being prepared for a catastrophic emergence of widespread multi-drug-resistant infections (sometimes referred to as 'insurance value', see section 3.22). To reflect this, EEPRU provided additional exploratory scenario analyses to reflect a situation in which a new multi-drug-resistant pathogen emerges, against which ceftazidime–avibactam is the only effective treatment. In the absence of evidence to inform the probability, timing and impact of such an event, EEPRU used the following estimates suggested by a committee member with specialist expertise in infectious disease:

- probability of the emergence of highly resistant pathogen(s): 1%
- time to event: 10 years
- number of people affected in the first year: 25
- annual growth in number of infections: 20%.

EEPRU explored the impact of varying these parameter estimates using plausible ranges provided by the same committee member. EEPRU maintained the susceptibility to ceftazidime–avibactam at 90% over the long term. For the scenario in which a new multi-drug-resistant organism emerged, EEPRU presented incremental net health benefit results for infection sites separately. It was unable to present the overall population-level results across all infection sites because it lacked evidence for the proportion of patients for each site. The committee would have preferred to see results for the total population. It was also concerned that the scenario did not include the pathogens modelled in the base-case analysis. The committee considered that resistance to comparators was likely to increase, but that EEPRU's scenario analysis was highly

uncertain, and was not entirely relevant to the population under consideration. The committee recognised EEPRU's challenges when modelling the unknown. It concluded that the model underestimates the benefits of ceftazidime–avibactam by not accounting for increased resistance to comparators.

Approximately 20% of people would not be offered colistin or an aminoglycoside, even if no other effective antimicrobial were available

3.16 In its base-case model, EEPRU assumed that a proportion of patients would have infections resistant to all existing antimicrobials other than colistin- or aminoglycoside-based regimens. However, consultation comments on EEPRU's report highlighted that some people cannot tolerate the renal toxicity associated with colistin and aminoglycosides, or tolerate renal replacement therapy. So, they would not be offered these treatments, even if no other therapy were available. Instead, these people would be offered 'multi-drug salvage therapy', a regimen combining multiple agents: no 1 drug would be expected to be effective in isolation, but there could be some benefit when used in combination. EEPRU did not account for this in its base-case model. In response to the consultation comments, EEPRU did a scenario analysis to estimate the incremental benefit of ceftazidime–avibactam in this subgroup of patients. Rather than modelling this population separately, EEPRU derived a weighted average incremental benefit that accounted for the proportion of the total treated population whose infection would be susceptible to colistin or aminoglycosides but would not be offered these treatments because of the high risk of renal toxicity. In the absence of empiric evidence, EEPRU based its analysis on advice from the committee, which suggested that 20% to 40% of patients would be unable to take colistin or aminoglycoside-based regimens. The committee understood that the risk of renal toxicity is lower with aminoglycosides than with colistin (see section 3.8). A committee member with specialist expertise in infectious diseases thought that the proportion of people unable to take colistin would be close to 40%, but recognised that renal dosing (adjusting the

dose based on renal capacity, to reduce the risk of renal toxicity) would allow colistin to be offered to some of these people. The committee heard from a clinical expert that approximately 5% to 10% of people would be unable to take aminoglycosides. On balance, the committee concluded that the most plausible scenario was the one in which EEPRU assumed that 20% of people cannot have colistin or aminoglycosides, even if no other effective antimicrobial were available. In the empiric treatment setting, this represented 20% of the total treated population. In the microbiology-directed setting, EEPRU assumed that clinicians would consider colistin or aminoglycosides as a treatment option for the 35% of people whose infections would be resistant to non-colistin-based or non-aminoglycosides-based regimens. This means that the proportion of people in the overall microbiology-directed setting who would not be offered colistin or aminoglycosides was 7%.

The model does not fully capture additional elements of benefit that are important for antimicrobials

3.17 Several benefits that are important for antimicrobials (see sections 3.18 to 3.22) were not fully captured in EEPRU's analysis. Some of these would increase the estimated incremental benefits of ceftazidime–avibactam. The committee considered the extent to which each element of value was captured in EEPRU's model.

Ceftazidime–avibactam does not offer spectrum value

3.18 Spectrum value refers to the benefits of a new, effective, narrow-spectrum antimicrobial replacing broad spectrum antimicrobials, reducing problems of antimicrobial resistance associated with their use. EEPRU did not model spectrum value for ceftazidime–avibactam because it considered that ceftazidime–avibactam has a broad spectrum of activity. The clinical experts agreed with EEPRU's assumption that spectrum value was unlikely to be relevant for ceftazidime–avibactam because under a policy of responsible antimicrobial stewardship, it would replace treatments with

a similar spectrum of activity. The committee concluded spectrum value was not a source of benefit in this evaluation.

Ceftazidime–avibactam is unlikely to offer transmission value, but this is a source of uncertainty

3.19 Transmission value refers to the benefits of a new antimicrobial reducing transmission of a given pathogen from people who have had treatment to other people, and reducing the incidence of resistant infection. EEPRU did not include transmission value in its analysis, because changes impacting transmission are broad and can have opposite effects. For example, if ceftazidime–avibactam reduced the length of hospital stay it could reduce transmission, but if it reduced mortality this could also increase the length of hospital stay and increase transmission. EEPRU was also advised by its clinical experts that pathogens may remain in the gut even after successful treatment and continue risking transmission. A committee member with specialist expertise in infectious disease agreed. So, the overall direction of effect is unclear and there is a lack of evidence to support one direction or the other. The committee concluded that transmission value was unlikely to be a source of benefit but acknowledged that this was an area of uncertainty.

The enablement value of ceftazidime–avibactam is not fully captured

3.20 Enablement value refers to the benefits of being able to perform medical procedures because of new antimicrobials for resistant infections with few treatment options. When possible, EEPRU included some aspects of this value in its analysis, including the improved treatment of postoperative infections, and the benefits of releasing hospital resources, that would otherwise be used for treating infections, to enable healthcare and procedures in other patients. It did not include other aspects of enablement, such as increasing the number of procedures that are able to go ahead in people whose infections are treated, or keeping wards open during an outbreak. The committee was aware that treating a single multi-drug-resistant infection can be costly because staff allocated to this

person are unable to care for other people, to reduce the risk of transmission. It noted that the reduced renal toxicity of ceftazidime–avibactam compared with antimicrobials that clinicians would otherwise offer would free up hospital resources by reducing the number of people needing dialysis and enabling other procedures to go ahead. The committee noted that enabling procedures to go ahead was a benefit of ceftazidime–avibactam. The committee noted that improvements in medicine meant that the number of procedures and interventions including organ transplantation and new cancer treatments has increased in recent years and will continue to increase in the next 5 to 10 years. The committee recognised that the magnitude of ceftazidime–avibactam's enablement value depends, in part, on the value of the 'enabled' procedures. The committee was also aware that the model also did not capture the value provided by ceftazidime–avibactam of reducing the staff time and other hospital resources that are lost because of procedures cancelled because of infection. The committee acknowledged the challenges in modelling enablement value and concluded that EEPRU's model had not fully captured enablement value.

The diversity value of ceftazidime–avibactam is not captured

3.21 Diversity value refers to the benefits of new antimicrobials diversifying the range of treatments available, thereby reducing use of individual treatments. EEPRU did not model strategies involving diverse prescribing, which it considered inappropriate in high-value clinical scenarios without effective alternative treatments. Outside of high-value clinical scenarios, EEPRU considered that ceftazidime–avibactam should not be used, to avoid developing resistance associated with other antimicrobials. The clinical experts suggested that EEPRU's model underestimated diversity value, explaining that ceftazidime–avibactam will reduce use of carbapenems, and provide an alternative treatment option when there are supply issues with other antimicrobials. The committee noted that diversity value is important when treating severe infections in intensive care units, because people are also likely to have organ failure and have few

treatment options. It is therefore important to have a diverse range of antimicrobials available in this setting, because relying on a limited range of antimicrobials will drive resistance. The committee concluded that diversity value was an uncaptured value that would increase the total net health benefits of ceftazidime–avibactam.

The insurance value provided by ceftazidime–avibactam is not fully captured

3.22 Insurance value refers to the benefits of reserving a new antimicrobial until resistance eliminates current alternatives as options, or the benefits of being prepared for a catastrophic emergence of widespread multi-drug-resistant infections against which only the new antimicrobial is effective. The committee was aware that EEPRU did not model a scenario in which ceftazidime–avibactam is held back (that is, not used at all to preserve its effectiveness). It recalled EEPRU's scenario in which a new multi-drug-resistant pathogen emerges against which ceftazidime–avibactam is the only effective treatment (see section 3.15). The committee noted that these analyses were based on adopting a risk-neutral perspective but agreed that a risk-averse perspective is likely to be more appropriate for estimating the insurance value of an antimicrobial. Being risk-averse means paying more than the expected value of a product (in this case, a new antimicrobial) to insure against future unwanted future events. However, the committee acknowledged that it had no basis to determine the additional value that the NHS would be willing to pay to avoid a situation in which an infection emerged that was resistant to all available treatments. The committee concluded that EEPRU's model had not fully captured the potential 'insurance value' of ceftazidime–avibactam.

Incremental net health benefits estimate

The incremental net health benefit of ceftazidime–avibactam is estimated to be 8,880 QALYs over the 20-year modelled time horizon

3.23 The committee recalled its preferred assumptions from the options presented by EEPRU:

- The network meta-analysis of susceptibility studies used in EEPRU's base-case economic model was an appropriate source of evidence for clinical outcomes (see section 3.7).
- OXA-48 producing *Enterobacterales* infections are likely to increase over the modelled time horizon, that is, follow a persistent growth trend (see section 3.13).
- The clinical advisers' classification of infection site is more appropriate than the UKHSA's classification of infection site for estimating the number of people currently eligible for ceftazidime–avibactam (see section 3.12).
- Resistance to ceftazidime–avibactam will increase by 5% over the 20-year modelled time horizon (see section 3.14).
- 20% of patients would not be offered colistin or aminoglycoside-based treatment regimens (see section 3.16).

Using these assumptions, the incremental net health benefit of ceftazidime–avibactam was approximately 3,700 QALYs. The committee also recalled its conclusions about the benefits of ceftazidime–avibactam that had not been captured in EEPRU's analysis, specifically:

- The population for whom ceftazidime–avibactam is suitable is likely to be 2 to 3 times larger than EEPRU's estimate (see section 3.10). The committee understood that increasing the population size would increase the incremental benefit of ceftazidime–avibactam. On balance, the committee concluded the increased population size would double the incremental QALYs for ceftazidime–avibactam.

- The model did not capture all elements of value. The committee identified that enablement value, diversity value and insurance value were not fully captured (see sections 3.17 to 3.22). It also identified that the model had underestimated the benefits of ceftazidime–avibactam by not accounting for increased resistance to comparators over time (see section 3.15). The committee concluded that the estimate of incremental QALYs should be increased by a further 20% to account for uncaptured value.

The committee concluded that the incremental net health benefit of ceftazidime–avibactam would be approximately 8,880 QALYs over the 20-year modelled time horizon. It acknowledged that there was a large degree of uncertainty around this estimate because of uncertainties in the model results and in estimating uncaptured benefits (see paragraph 3.24).

There is uncertainty in the analysis and further research is encouraged

3.24 EEPRU's probabilistic sensitivity analysis resulted in a broad range of estimates of incremental QALYs. This indicates that uncertainty around the parameter values in the model affects the population-level value of ceftazidime–avibactam. The committee recalled several areas of uncertainty in the evaluation that relate to the model structure and to the assumptions made by EEPRU in the absence of evidence. These included the association between in vitro susceptibility and clinical outcomes, the trends in antimicrobial usage and resistance over time, the limitations of the data from the UKHSA SGSS to estimate the size of the population for whom ceftazidime–avibactam is suitable, and the uncaptured benefits. The committee concluded that the QALY estimates were associated with significant uncertainty, and encouraged research to further develop best practice in the health economic evaluation of antimicrobials.

Conclusion

The total benefits of ceftazidime–avibactam assigned to each year of the contract period should be a minimum of 530 QALYs

3.25 Having concluded that the total benefits over the 20-year time horizon would be approximately 8,880 QALYs, the committee considered what proportion of this should be assigned to a 10-year contract period. It considered that this should be at least as much as the rewards typically earned by companies during the first 10 years of marketing a non-antimicrobial. Assigning a lower proportion would not address the issues of market failure for new antimicrobials nor create a 'pull incentive' for investment. EEPRU presented the committee with evidence that the proportion of benefits of non-antimicrobial drugs in their first 10 years on the market is about 60%. The committee's view was that the proportion of benefits that should be assigned to a 10-year contract period ranged from 60% to 100%. The committee concluded that the proportion of QALY benefits to assign to each year of the 10-year contract period should be a minimum of 60%, resulting in a minimum of 530 QALYs per year.

Ceftazidime–avibactam should only be offered if there are few alternative treatment options, after advice from a specialist in microbiology or infectious disease

3.26 The committee agreed that good antimicrobial stewardship is extremely important to preserve the effectiveness of ceftazidime–avibactam and to minimise the risk of developing resistance. It was aware of NICE's guideline on antimicrobial stewardship. The committee agreed that ceftazidime–avibactam should be reserved for people with few alternative treatment options, either because their infection is expected, or has been confirmed to be, resistant to other antimicrobials, or because there are serious concerns about the toxicity, or availability of alternative treatments (see section 3.16). The committee considered that ideally clinicians would offer ceftazidime–avibactam only after microbiology susceptibility or gene

tests have confirmed that the pathogen is resistant to alternative treatment options and susceptible to ceftazidime–avibactam. However, it recognised that having these test results before starting treatment was not always possible, for example if a person's condition is clinically unstable with a fast-progressing infection that is not responding to other antimicrobials. The committee agreed that it would be appropriate to offer ceftazidime–avibactam in the absence of test results, only if clinicians strongly suspect that the infection will be susceptible to ceftazidime–avibactam, and there are few alternative treatment options. The committee noted that the estimates of incremental net health benefit for ceftazidime–avibactam were based on using it under these conditions. The committee was aware that the marketing authorisation for ceftazidime–avibactam states that it should be offered 'only after consultation with a physician with appropriate experience in the management of infectious diseases' and agreed that this was essential to limit antimicrobial resistance. The committee concluded that ceftazidime–avibactam should only be offered when there are few alternative treatment options, and only when microbiological susceptibility or gene testing has confirmed that the infection is susceptible to ceftazidime–avibactam, or when there is an urgent need to treat an infection expected to be susceptible to ceftazidime–avibactam and results of microbiological or gene tests are not yet available.

4 Recommendations for research

4.1 NICE recommends further research to develop best practice in the health economic evaluation of antimicrobials in the UK, Europe and globally. This includes:

4.2 Developing methods to model and quantify the additional elements of benefit of new antimicrobials, including but not limited to spectrum, transmission, enablement, diversity and insurance value.

4.3 Determining the relationship between a pathogen's in vitro susceptibility to an antimicrobial treatment and relevant outcomes in people with multi-

drug-resistant bacterial infections. Data should include patient identification to allow linkage. It should reflect the site of culture sample, state the probable site of infection, identify the pathogen, identify the mechanism of antimicrobial resistance, and record antimicrobial treatment. Relevant clinical outcomes may include but are not limited to mortality (including all-cause mortality and mortality attributable to the infection), clinical cure (resolution of the signs or symptoms of the infection meaning that no further antimicrobial therapy is needed) and microbiological eradication. Relevant safety outcomes include acute kidney injury, renal replacement therapy, colonisation with multi-drug-resistant pathogen following treatment, and *Clostridioides difficile* infection. Relevant resource-use outcomes include length of hospital stay by ward type and duration of treatment. Ideally a range of different antimicrobial treatments would be included in a single study, to ensure consistency in laboratory methods and clinical breakpoints.

4.4 Establishing better methods to synthesise evidence from in vitro antimicrobial susceptibility studies. This could include:

- Establishing whether the different laboratory methods and clinical breakpoints used to assess antimicrobial susceptibility, which are set by different organisations (for example, European Committee on Antimicrobial Susceptibility Testing [EUCAST] and Clinical and Laboratory Standards Institute [CLSI]), are interchangeable.
- Establishing whether it is preferable to use clinical breakpoints at the same time as to sample collection, or whether it is acceptable to apply newly published breakpoints to historic data.
- Developing a tool to assess the quality of in vitro antimicrobial susceptibility studies.

- Establishing if and how changes to laboratory methods used to assess susceptibility affect synthesising data from different antimicrobial susceptibility studies.

- Developing reporting guidelines (similar to those provided by PRISMA and CONSORT) to ensure studies of antimicrobial susceptibility are reported clearly and comprehensively.

5 Recommendations for data collection and antimicrobial surveillance

5.1 The contract between the company and NHS England and NHS Improvement requires the company to participate in the UK Antimicrobial Registry (UKAR), developed by the British Society for Antimicrobial Chemotherapy (BSAC) in partnership with the University of Aberdeen. This registry will provide information on the relationship between patterns of antimicrobial usage and emergence of resistance in the UK, and will provide quantitative data on the clinical and safety outcomes of antimicrobials. The following information should be captured as part of the UKAR registry and through other surveillance and monitoring programmes in England for all antimicrobials, for example Blueteq:

- Site of clinical infection

- Type of sample (for example, sputum, tracheal, bronchial wash, pleural aspirate).

- Pathogen and mechanism of antimicrobial resistance:

  – When the results of microbiological or gene tests are available: record the confirmed pathogen, confirmed resistance mechanism and the antimicrobial agents the pathogen is susceptible to.

  - If the antimicrobial is used ‘empirically’ (that is, when results of microbiological or gene tests are not yet available): record the suspected pathogen and resistance mechanism.

  - Data should capture whether the confirmed pathogen and resistance mechanism differed from that suspected in the empirical setting.

- Clinical outcomes including but not limited to mortality (including all-cause mortality and mortality attributable to the infection), clinical cure (resolution of the signs or symptoms of the infection meaning that no further antimicrobial therapy is needed) and microbiological eradication.

- Safety outcomes including acute kidney injury, renal replacement therapy, colonisation with multi-drug-resistant pathogen following treatment and *C. difficile* infection.

- Resource use outcomes including length of hospital stay by ward type and duration of treatment.

5.2 NICE recommends that in the further development of UK health data infrastructure, such as hospital electronic health records and the UK Health Security Agency’s (UKHSA; formerly Public Health England [PHE]) surveillance systems for antimicrobial resistance, consideration is given to new data fields relating to clinically significant infections. Information on whether the clinician suspects there is a clinical infection that requires antimicrobial treatment and the site of the suspected clinical infection, for example, would provide important evidence to estimate the number of people eligible for new antimicrobial therapies in the UK.

Amanda Adler

Chair, antimicrobials evaluation committee

April 2022

6 Antimicrobials evaluation committee members and NICE project team

Antimicrobials evaluation committee members

The antimicrobials evaluation committee was convened to test a new health technology evaluation process on 2 antimicrobial drugs. The committee has 18 members, including 12 members from other NICE committees and 6 members with specialist expertise in infectious disease.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of the committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

The antimicrobial evaluation was assigned to a team consisting of a technical lead, a technical adviser, several senior advisers and a project manager.

Caroline Bregman
Technical lead

Sophie Cooper
Technical adviser

Jacoline Bouvy, Nick Crabb, Colm Leonard
Senior advisers

Charlotte Downing
Project manager

ISBN: [to be added at publication]