

Cefiderocol for treating severe drug-resistant gram-negative bacterial infections

Antimicrobial resistance guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients.

The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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This guidance replaces HTE2.

1 Recommendations

1.1 Cefiderocol is recommended, within its marketing authorisation, as an option for treating severe drug-resistant infections caused by gram-negative bacteria. This includes, but is not limited to, infections caused by metallo-beta-lactamase-producing *Enterobacteriales*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. Clinicians should follow advice from specialists in microbiology or infectious disease and offer cefiderocol only if there are no suitable alternative treatment options.

The decision to offer cefiderocol should be guided by results from tests for microbiological susceptibility and mechanisms of resistance that confirm that the infection is susceptible to cefiderocol, and not susceptible to other suitable antibiotics. If these results are not yet available, cefiderocol may be offered, but only if the infection:

- needs urgent treatment, and
- is expected to be susceptible to cefiderocol and not to other suitable antibiotics.

As well as considering susceptibility, judgements about whether an alternative treatment is suitable may take account of concerns about its toxicity, availability or interactions with other drugs, and its spectrum of activity.

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

1.2 Because of the uncertainty in the estimates of the value of cefiderocol to the NHS in England, NICE encourages research to further develop best practice in the health economic evaluation of antimicrobials (see sections 5 and 6).

2 Commercial arrangement

- 2.1 Under its contract with NHS England, the company will receive quarterly payments that are not linked to the volume of cefiderocol supplied to the NHS. The value of the payments was informed by the NICE committee's estimate of the benefits of cefiderocol, measured in quality-adjusted life years (QALYs) (see section 4.25 of the committee discussion). It has been agreed for a 3-year period, with an option to extend up to 10 years.
- 2.2 Purchasing authorities will acquire cefiderocol using an agreed confidential invoice price. NHS England will subtract the costs of these purchases from its quarterly payments to the company.
- 2.3 NHS organisations can find the confidential invoice price for cefiderocol in the NHS Pharmacy Catalogue. Non-NHS organisations can contact contact@shionogi.eu for details.
- 2.4 The contract between the company and NHS England also stipulates conditions relating to good antimicrobial stewardship, manufacturing and environmental practices; monitoring for emerging resistance; and ensuring supply of cefiderocol.

3 Information about cefiderocol

3.1 Cefiderocol is a siderophore cephalosporin. It inhibits gram-negative bacterial cell wall synthesis by binding to penicillin-binding proteins. Cefiderocol 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

3.2 Cefiderocol (Fetcroja, Shionogi) is indicated 'for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options'.

Dosage in the marketing authorisation

3.3 The dosage schedule is available in cefiderocol's summary of product characteristics.

4 Committee discussion

The antimicrobials evaluation committee considered the evidence submitted by Shionogi (the company that manufactures cefiderocol) 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

4.1 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 have historically 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 limited treatment options for carbapenemase-mediated resistance. Carbapenemase enzymes are grouped into 2 main classes: serine carbapenemases and metallo-beta-lactamases (MBLs). Cefiderocol is active against both classes of carbapenemases in gram-negative bacteria. The main serine carbapenemases in the UK are *Klebsiella pneumoniae* carbapenemase and oxacillinases, in particular OXA-48. The main MBLs in the UK are New Delhi MBL (NDM), Verona integrated-encoded MBL (VIM) and imipenemase (IMP).

Multi-drug-resistant infections reflect an unmet need, and are a

significant burden on patients and their families

4.2 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 limited treatment options. They highlighted the negative impact that infections have on people's psychological wellbeing because they may be hospitalised in isolation. 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. The patient experts emphasised that the adverse effects of existing antimicrobials can significantly affect quality of life. The committee concluded that there was an unmet need, and that 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

4.3 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 antimicrobial 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-drug-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 antimicrobial stewardship, coupled with a limited period of market exclusivity, during which companies expect to generate the most revenue. When generic antimicrobials 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

4.4 In 2018, EEPNU 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. This evaluation was part of a project to test a new reimbursement model 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 or a subscription-based contract). Instead, the payments are based on the benefits that the antimicrobial offers to patients and to the NHS over time, which this NICE evaluation estimated (see section 4.25). This estimate informed commercial discussions between NHS England and the company that manufactures cefiderocol. The subscription-based contract between the company and NHS England 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 cefiderocol 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 EEPNU using a 20-year time horizon (see section 4.9), 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 a 10 year contract period.

Clinical evidence

The clinical evidence has limited generalisability to multi-drug resistant infections caused by MBL-producing *Enterobacteriales*

or *P. aeruginosa*

4.5 EEPRU's literature review identified 3 randomised clinical trials comparing cefiderocol with imipenem–cilastatin, meropenem, and best available therapy. Two of the clinical trials included only people with carbapenem-susceptible infections, whereas this evaluation focusses on using cefiderocol to treat severe, multi-drug-resistant infections. The third trial included people with carbapenem-resistant infections, but very few had MBL-mediated resistance, the only resistance mechanism included in EEPRU's economic model (see [section 4.10](#)). Two of the trials used a non-inferiority design and the third did not include tests for statistical significance. EEPRU identified 3 observational studies in people with MBL-producing drug-resistant infections treated with cefiderocol, but none reported data for comparison treatments. The observational studies also had small sample sizes and included people with a diverse range of characteristics that likely would have affected their prognosis and how well their infections responded to treatment. The committee concluded that the available clinical trials and observational studies have limited generalisability when evaluating cefiderocol in multi-drug-resistant infections caused by MBL-producing *Enterobacterales* or *Pseudomonas aeruginosa*.

Using data from in vitro susceptibility studies as a surrogate endpoint for clinical outcomes is reasonable, but the results are uncertain

4.6 Because of the lack of generalisable clinical trials or observational data specifically for MBL-producing drug-resistant infections, EEPRU assessed the relative clinical effectiveness of cefiderocol compared with other antibiotics using the laboratory-assessed susceptibility of a pathogen to antimicrobial treatment instead of using direct evidence on patient outcomes (see [section 4.8](#) for the comparator treatments in EEPRU's model). 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' is a threshold of the antimicrobial concentration 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 report linking in vitro susceptibility data to clinical outcomes, but the evidence did not relate to the pathogens and resistance mechanisms of interest in this evaluation. EEPRU used the results of 2 published studies it 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 4.10](#)). To model outcomes in the 'microbiology-directed treatment setting', EEPRU used established methods to elicit information from experts to characterise the relationship between susceptibility data and clinical outcomes. 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 that outcomes did not depend on the resistance mechanism causing the infection. Results were available from between 5 and 7 experts, depending on the question. Consultation comments on EEPRU's report suggested that these assumptions were not plausible and introduced uncertainty into the modelling. Consultees commented that in vitro data would not reflect a patient's clinical factors affecting response to treatment or whether the tissue penetration of the antimicrobial differs by infection site. The company noted that in vitro susceptibility would not reflect cefiderocol's potentially improved tissue penetration over its comparators, which the company suggested would increase its relative effectiveness. The clinical experts at the committee meeting confirmed that there are many factors other than susceptibility and those identified by EEPRU that affect treatment efficacy and outcomes. The consultees highlighted the small sample size of the expert elicitation. The clinical experts explained that, in the absence of alternative evidence and better estimates, using susceptibility as a predictor of clinical outcomes in EEPRU's model was reasonable. The committee concluded that susceptibility was a reasonable surrogate for clinical outcomes but recognised that it introduced uncertainty into the model.

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

4.7 EEPRU compared pathogen susceptibility to cefiderocol with susceptibility to other antimicrobials. It used a network meta-analysis that combined data from the 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 cefiderocol and to comparators. EEPRU considered the EUCAST laboratory methods and breakpoints to be the most applicable to England, because the British Society for Antimicrobial Chemotherapy recommends using EUCAST methods and breakpoints in clinical practice. None of the susceptibility studies identified in EEPRU's literature review used EUCAST laboratory methods. Some studies reported data for both EUCAST and CLSI breakpoints, some reported only EUCAST breakpoints, and some reported only CLSI breakpoints. In its base-case economic model, EEPRU used a network meta-analysis of studies that applied EUCAST breakpoints to data generated using CLSI laboratory methods. This was supplemented by the UKHSA data, which EEPRU assumed used EUCAST methods because it was collected in the UK. EEPRU did scenario network meta-analyses to test the impact of using different studies and applying different clinical breakpoints:

- One scenario used only the studies that used both CLSI laboratory methods and CLSI breakpoints.
- Another scenario included separate evidence networks for cefiderocol and fosfomycin, also using CLSI laboratory methods and breakpoints. EEPRU combined these with the UKHSA data, which did not include either of these 2 therapies, to generate relative effectiveness estimates for all the comparators.

There was no consensus among consultees on whether EEPRU's approach of mixing laboratory methods and breakpoints in its base-case network meta-analysis was valid or invalid. The committee preferred using EUCAST breakpoints because they are the most applicable to England. It agreed that it was acceptable to apply EUCAST breakpoints to data generated using CLSI laboratory methods, because the EUCAST and CLSI laboratory methods are sufficiently similar. 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

4.8 Current standard care for treating infections suspected or confirmed to be caused by MBL-producing *Enterobacterales* or *Pseudomonas aeruginosa* includes a range of antimicrobials. Treatment choice depends on the infection site, the pathogen, whether microbiological testing has confirmed the resistance mechanism, and whether the pathogen has additional mechanisms of resistance. For *Enterobacterales* infections, the comparators were aminoglycosides and aztreonam, tigecycline, or fosfomycin with colistin. For *Pseudomonas aeruginosa* infections, comparators were fosfomycin with colistin, or meropenem. When more than 1 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 of people with an infection that was:

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

The clinical experts on the committee and at the meeting agreed that it was appropriate to consider colistin and aminoglycosides separately from other antimicrobials because they are associated with a risk of renal toxicity, which is higher with colistin than aminoglycosides. The clinical experts 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 4.16](#)). The committee concluded that the comparators and classification of comparators in EEPRU's analyses were appropriate.

EEPRU modelled benefits of cefiderocol in 2 stages: at the individual patient level and at the population level

4.9 EEPRU quantified the benefits of cefiderocol in 2 stages. First, it developed a new decision analytic model to estimate the costs and benefits of cefiderocol over a patient's lifetime (the 'patient-level model'). It modelled the clinical effectiveness, safety, quality of life, costs and resource use associated with cefiderocol 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 cefiderocol related only to the use of healthcare resources. To convert any cost savings (or losses) associated with cefiderocol (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 cefiderocol, EEPRU 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 cefiderocol and other antimicrobials. EEPRU modelled the benefits of cefiderocol over a 20-year time horizon. This allowed EEPRU to estimate the long-term costs and benefits of cefiderocol at the population level.

The modelled population is smaller than the population that would be offered cefiderocol in practice

4.10 The marketing authorisation of cefiderocol is broad. EEPRU's analysis was narrower than the marketing authorisation and focused on populations in which it expected cefiderocol to have the greatest clinical benefit, and referred to these as 'high-value clinical scenarios'. EEPRU divided the clinical scenarios into 2 treatment settings: 'empiric' and 'microbiology-directed'. '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 setting was 'microbiology-directed' and referred to an identified organism with tested and confirmed microbiological susceptibility. EEPNU included several high-value clinical scenarios in its patient-level analysis: hospital-acquired pneumonia and ventilator-associated pneumonia treated empirically; and complicated urinary tract infection, hospital-acquired pneumonia, and ventilator-associated pneumonia treated in the microbiology-directed setting. EEPNU focused on infections with *Enterobacterales* and *Pseudomonas aeruginosa* with MBL mechanisms of resistance. In its population-level model, EEPNU included additional groups of patients in which cefiderocol is expected to have clinical benefit and be used in practice: people with bloodstream and intrabdominal infections and people with infections caused by *Stenotrophomonas maltophilia*. Based on clinical advice, EEPNU considered that cefiderocol would be suitable for only 15% of *Stenotrophomonas maltophilia* infections, which the committee agreed was a reasonable assumption. EEPNU's estimates of the number of people eligible for cefiderocol ranged between 600 and 1,300 people per year in England. A committee member with specialist expertise in infectious disease noted that data on current cefiderocol usage in England may not accurately reflect population size. This is because temporary shortages of another antimicrobial, ceftolozane–tazobactam, has likely led to increased use of cefiderocol that would not be sustained in future. The company noted that because cefiderocol was a relatively new therapy, current usage data could underestimate patient numbers, and use would increase as cefiderocol becomes more established in clinical practice. The committee agreed that data on usage was not reliable for verifying EEPNU's population estimates. Consultation comments on EEPNU's report suggested that cefiderocol is effective against, and would be used to treat, pathogens and resistance mechanisms that EEPNU had not included in either its patient- or population-level analysis. For example, infections caused by *Acinetobacter baumannii* with MBL resistance mechanisms or pathogens with serine carbapenemase-mediated resistance against which other treatment options are not available or appropriate. Consultees highlighted the importance of cefiderocol 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 cefiderocol. The committee concluded that the current population size is likely to be at least 2 times bigger than EEPRU's estimate.

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

4.11 When modelling benefits of cefiderocol at the population level, EEPRU included additional groups of patients in which cefiderocol is expected to have clinical benefit and be used in practice (see [section 4.10](#)). Because EEPRU did not include these groups in its patient-level model, it was unable to estimate the patient-level QALY gains. 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. It assumed that QALY gains in people with intra-abdominal infections were the same as those in people with complicated urinary tract infections. For *Stenotrophomonas maltophilia* infections, it assumed that the QALY gains in each infection site reflected a weighted average of those in the same infection site for *Enterobacterales* and *Pseudomonas aeruginosa*. 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, the committee recognised that EEPRU's assumptions introduced further uncertainty in the model, but concluded that it is reasonable to generalise incremental benefits of cefiderocol 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 cefiderocol

4.12 EEPRU estimated the number of people currently eligible for cefiderocol 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 and so is uncertain, as confirmed by the clinical experts at the committee meeting. The clinical experts explained that the UKHSA SGSS data represent isolates classified as susceptible to cefiderocol through laboratory testing, rather than infections treated by cefiderocol in practice. Therefore, the UKHSA SGSS data may overestimate the eligible population because it includes isolates that may not cause significant clinical illness needing antimicrobial treatment. The committee also heard that the UKHSA SGSS data might underestimate the eligible population because not all hospitals have a microbiology laboratory, and the data submitted to the SGSS from some 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. The committee also noted that each isolate in the database was tested for several MBL resistance mechanisms. EEPRU assumed that each *Enterobacterales* specimen was tested for 3 resistance mechanisms and each *Pseudomonas aeruginosa* specimen was tested for 4, so divided the number of isolates by 3 and 4 to estimate the number of eligible people. The committee agreed that this introduced further uncertainty in the estimates of the population size. EEPRU explored 2 ways of establishing the infection site from the SGSS data: based on the UKHSA's classification of the specimens or 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 cefiderocol, 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 600 people when using the UKHSA's classification, and 1,300 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 infections with MBL resistance mechanisms is likely to continue increasing in the long term

4.13 To forecast how the population eligible for cefiderocol might change over the

20-year modelled time horizon, EEPNU used historical data on population size for people infected with *Enterobacterales* and *Pseudomonas aeruginosa* with MBL resistance mechanisms provided by the Antimicrobial Resistance and Healthcare Associated Infections national reference laboratory. EEPNU received no data for *Stenotrophomonas maltophilia*. EEPNU excluded data from before October 2012 because of small patient numbers, and excluded data after March 2018 because of an anomalous decrease in reporting caused by changes in guidelines. Based on visual comparisons and statistical goodness-of-fit measures, EEPNU selected different approaches to modelling future population sizes for people infected with each pathogen. For *Enterobacterales*, it applied 2 alternative methods 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. EEPNU provided base-case economic analyses including both approaches. For *Pseudomonas aeruginosa*, EEPNU found no evidence of population growth in the historical data and so assumed that the number of people with drug-resistant infections caused by this pathogen annually would remain the same over the modelled time horizon. The clinical experts noted that this was not plausible, and that they would expect to see growth in the population of people with MBL-producing *Pseudomonas aeruginosa* over time. For *Stenotrophomonas maltophilia*, EEPNU estimated population growth to be a weighted average of the growth rates for *Enterobacterales* and *Pseudomonas aeruginosa*. The committee recognised that although there was considerable uncertainty in the 2 forecasting approaches applied to the *Enterobacterales* population, the persistent growth model best fitted the data and was the more clinically plausible. The committee concluded that it was appropriate to assume that the population size of MBL-producing *Enterobacterales* infections would continue to grow over the modelled time horizon rather than stabilise. The committee also concluded that assuming no growth in the population size of people with MBL-producing *Pseudomonas aeruginosa* infections would likely underestimate the population-level incremental net health benefits of cefiderocol.

Resistance to cefiderocol is expected to increase by approximately 5% over the next 20 years

4.14 Based on evidence that resistance develops to new antimicrobials as usage increases, EEPNU assumed that resistance to cefiderocol would also increase over the model's 20-year time horizon. EEPNU 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 0.04% in *Enterobacterales* and 0.16% in *Pseudomonas aeruginosa* over 20 years. EEPNU believed that these values underestimated true resistance and explored 4 alternative assumptions in its base-case model: resistance to cefiderocol reaching 1%, 5%, 10% or 30% after 20 years. EEPNU and the company agreed that 30% was an extreme estimate. The clinical experts explained that if principles of good antimicrobial stewardship were followed, then the increase in resistance to cefiderocol would be low. However, wider use of cefiderocol outside of the UK would cause resistant pathogens to emerge that would eventually appear in England. A committee member with specialist expertise in infectious disease noted that resistance would not be expected to exceed 10% over the 20-year modelled time horizon and would more likely be 5%. The committee concluded that it was reasonable to assume a 5% increase in resistance to cefiderocol 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

4.15 In its base-case model, EEPNU assumed that resistance to the comparators remains constant over time, because it found little evidence to inform extrapolations of current resistance rates. However, EEPNU 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 cefiderocol. 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 4.22). To reflect this, EEPRU provided additional exploratory scenario analyses to reflect a situation in which a new multi-drug-resistant pathogen emerges, against which cefiderocol 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 cefiderocol 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 also concluded that the model underestimates the benefits of cefiderocol 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

4.16 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 its treatment – renal replacement therapy. The comments noted that these people would not be offered these treatments, even if no other therapy were available. Instead, they would be offered 'multi-drug salvage therapy', a regimen combining multiple agents: no single 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 cefiderocol in this subgroup of patients. Rather than modelling this population separately, EEPRU derived a weighted average incremental benefit that accounted for the proportion of people whose infection would be susceptible to colistin or aminoglycosides but who 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 4.8). A committee member with specialist expertise in infectious diseases stated 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 function, 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 people whose infections would be resistant to non-colistin-based or non-aminoglycosides-based regimens, which differed by pathogen. This means that the proportion of people in the overall microbiology-directed setting who would not be offered colistin or aminoglycosides was 2% for *Enterobacteriales*, 14% for *Pseudomonas aeruginosa* and 8% for *Stenotrophomonas maltophilia*.

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

4.17 Several benefits that are important for antimicrobials (see sections 4.18 to 4.22) were not fully captured in EEPNU's analysis. Some of these would increase the estimated incremental benefits of cefiderocol. The committee considered the extent to which each element of value was captured in EEPNU's model.

Cefiderocol does not offer spectrum value

4.18 Spectrum value refers to the benefits of a new, narrow-spectrum antimicrobial replacing broad spectrum antimicrobials, reducing problems of antimicrobial resistance associated with their use. EEPNU did not model spectrum value for cefiderocol because it considered that cefiderocol has a broad spectrum of activity. The clinical experts agreed with EEPNU's assumption that spectrum value was unlikely to be relevant for cefiderocol 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.

Cefiderocol is unlikely to offer transmission value, but this is uncertain

4.19 Transmission value refers to the benefits of a new antimicrobial reducing transmission of a given pathogen from treated people to other people; the value is in reducing the incidence of resistant infection. EEPNU did not include transmission value in its analysis, because changes impacting transmission are broad and can have opposite effects. For example, if cefiderocol reduced the length of hospital stay, treatment could reduce transmission, but if treatment lengthened life this could increase length of hospital stay and increase transmission. EEPNU was advised by its clinical experts that even after successful treatment pathogens may remain in the gut which risks transmission; a committee member with specialist expertise in infectious disease agreed. The committee consider that 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 cefiderocol is not fully captured

4.20 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, EEPNU included some aspects of this value in its analysis, including the improved treatment of postoperative infections, and the benefits of freeing up 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 can go ahead in people whose infections are treated, or keeping wards open during an outbreak. The committee was aware that treating a single drug-resistant infection can be costly because, to reduce the risk of transmission, staff allocated to this person are unable to care for other people. It noted that the reduced renal toxicity of cefiderocol 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 agreed that this was an important source of value for cefiderocol because all its comparator treatments are associated with a high risk of renal toxicity, which would lead to the need for dialysis. The committee agreed that enabling procedures to go ahead was a benefit of cefiderocol. 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 and beyond. The committee recognised that the magnitude of cefiderocol's enablement value depends, in part, on the value of the 'enabled' procedures. The committee was also aware that the model did not capture the value provided by cefiderocol of reducing 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 EEPNU's model had not fully captured it.

The diversity value of cefiderocol is not captured

4.21 Diversity value refers to the benefits that new antimicrobials offer by 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. EEPRU considered that cefiderocol should not be used outside of high-value clinical scenarios to avoid developing resistance associated with other antimicrobials. The clinical experts suggested that EEPRU's model underestimated diversity value, explaining that cefiderocol will reduce use of carbapenems, and provide an alternative treatment option when there are supply issues with other antimicrobials. They also suggested that diversity value is particularly important when treating severe infections in intensive care units where resistance is more likely to develop because multiple pathogens and resistance mechanisms can be present at the same time, noting that cefiderocol is active against several different pathogens and resistance mechanisms. The committee noted that people in intensive care units may 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 agreed that cefiderocol offered diversity value because it is active against a range of different pathogens, and active against both types of carbapenemase-mediated resistance in gram-negative bacteria (see [section 4.1](#)). The committee concluded that diversity value was an uncaptured value that would increase the net health benefits of cefiderocol.

The insurance value provided by cefiderocol is not fully captured

4.22 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 drug-resistant infections against which only the new antimicrobial is effective. The committee was aware that EEPRU did not model a scenario in which cefiderocol is held back (that is, not used at all to preserve its effectiveness). It recalled EEPRU's scenario in which a new drug-resistant pathogen emerges against which cefiderocol is the only effective treatment (see [section 4.15](#)). 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 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 cefiderocol.

Incremental net health benefits estimate

The incremental net health benefit of cefiderocol is estimated to be 16,200 QALYs over the 20-year modelled time horizon

4.23 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 4.7).
- MBL-producing Enterobacterales infections are likely to increase over the modelled 20-year time horizon, that is, follow a persistent growth trend (see section 4.13).
- The clinical advisers' classification of infection site is more appropriate than the UKHSA's classification for estimating the number of people currently eligible for cefiderocol (see section 4.12).
- Resistance to cefiderocol will increase by 5% over the 20-year modelled time horizon (see section 4.14).
- 20% of patients would not be offered colistin or aminoglycoside-based treatment regimens (see section 4.16).

Using these assumptions, the incremental net health benefit of cefiderocol

was approximately 5,400 QALYs. The committee also recalled its conclusions about the benefits of cefiderocol not captured in EEPNU's analysis, specifically:

- The population for which cefiderocol is suitable is likely to be at least 2 times larger than EEPNU's estimate (see [section 4.10](#)). The committee understood that increasing the population size would increase the incremental benefit of cefiderocol. On balance, the committee concluded that the doubled population size would double the incremental QALYs for cefiderocol.
- The model did not capture all elements of value. EEPNU's assumption that there would be no growth in the population of people with MBL-producing *Pseudomonas aeruginosa* infections would likely underestimate the benefits of cefiderocol (see [section 4.13](#)). The committee identified that the model had underestimated the benefits of cefiderocol by not accounting for increased resistance to comparators over time (see [section 4.15](#)). It also identified that enablement value, diversity value and insurance value were not fully captured (see sections 4.17 to 3.22). The committee concluded that the estimate of incremental QALYs should be increased by a further 50% to account for uncaptured value.

The committee concluded that the incremental net health benefit of cefiderocol would be approximately 16,200 QALYs over the 20-year modelled time horizon, when the technology is used within its marketing authorisation and in line with the criteria in section 1.1. 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 [section 4.24](#)).

There is uncertainty in the analysis and further research is encouraged

4.24 EEPNU'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 cefiderocol. The committee recalled several areas of uncertainty in the evaluation that relate to the model structure and to the assumptions made by EEPNU 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 which cefiderocol is suitable, and the uncaptured benefits. The committee concluded that the QALY estimates were associated with significant uncertainty, and encouraged research to develop best practice in the health economic evaluation of antimicrobials (see sections 5 and 6).

Conclusion

The total benefits of cefiderocol assigned to each year of the contract period should be a minimum of 970 QALYs

4.25 Having concluded that the total benefits over the 20-year time horizon would be approximately 16,200 QALYs (see section 4.23), 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 drug. 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 the 10-year contract period ranged from 60% to 100%. The committee concluded that the proportion of QALY benefits to assign to each year of a 10-year contract period should be a minimum of 60%, resulting in a minimum of 970 QALYs per year.

Cefiderocol should only be offered if there are no suitable alternative treatment options, and after advice from a specialist in microbiology or infectious disease

4.26 The committee agreed that good antimicrobial stewardship is extremely important to preserve the effectiveness of cefiderocol and to minimise the risk of developing resistance. It was aware of NICE's guideline on antimicrobial

stewardship. The committee agreed that cefiderocol should be reserved for people with no suitable alternative treatment options, either because clinicians expect or have confirmed that the infection is resistant to other antimicrobials, or because there are concerns about the toxicity or availability of alternative treatments (see section 4.16). The committee considered that ideally clinicians would offer cefiderocol only after tests for microbiology susceptibility and mechanisms of resistance have confirmed that the pathogen is resistant to other suitable treatment options and susceptible to cefiderocol. 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 cefiderocol in the absence of test results, only if clinicians strongly suspect that the infection will be susceptible to cefiderocol, and not susceptible to other suitable antibiotics. The committee noted that the estimates of incremental net health benefit for cefiderocol were based on using it under these conditions. The committee concluded that, to limit antimicrobial resistance, cefiderocol should be offered only when there are no suitable alternative treatment options, and only when tests for microbiological susceptibility and mechanisms of resistance have confirmed that the infection is susceptible to cefiderocol and resistant to other suitable treatment options, or when there is an urgent need to treat an infection expected to be susceptible to cefiderocol and the results of these tests are not yet available.

5 Recommendations for research

5.1 NICE recommends further research to develop best practice in the health economic evaluation of antimicrobials in the UK, Europe and globally, as detailed in sections 5.2, 5.3 and 5.4.

5.2 Develop 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.

5.3 Determine 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 from which the sample was taken, 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 (signs and symptoms of infection resolved and no further antimicrobial therapy needed) and microbiological eradication. Relevant safety outcomes include acute kidney injury, renal replacement therapy, colonisation with multi-drug-resistant pathogen after treatment, and *Clostridioides difficile*. 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 consistent laboratory methods and clinical breakpoints.

5.4 Establish 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 sample collection, or whether it is acceptable to apply newly published breakpoints to historical 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.

6 Recommendations for data collection and antimicrobial surveillance

6.1 The contract between the company and NHS England 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 clinical and safety outcomes. The UKAR registry and other surveillance and monitoring programmes in England for antimicrobials, for example Blueteq, should capture the following information:

- Anatomical 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 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 signs or symptoms of infection and no further antimicrobial therapy needed) and microbiological eradication.
- Safety outcomes including acute kidney injury, renal replacement therapy, colonisation with a multi-drug-resistant pathogen after treatment, and *Clostridioides difficile*

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

6.2 NICE recommends that as the UK further develops its infrastructure for health data, such as hospital electronic health records and the UKHSA's surveillance systems for antimicrobial resistance, consideration is given to new data fields relating to clinically significant infections including those outlined above (see section 6.1). This data would help address uncertainties in the future when estimating the health benefits of new antimicrobial therapies in the UK.

Amanda Adler
Chair, antimicrobials evaluation committee
August 2022

7 Antimicrobials evaluation committee members and NICE project team

Antimicrobials evaluation committee members

The antimicrobials evaluation committee was convened to test a new process for health technology evaluation 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. NICE manages these conflicts of interest.

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

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

Technical lead: James Love-Koh

Technical adviser: Sophie Cooper

Senior advisers: Jacoline Bouvy, Nick Crabb, Colm Leonard

Project manager: Charlotte Downing

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