Cefiderocol for treating severe aerobic Gram-negative bacterial infections: technology evaluation to inform a novel subscription-style payment model

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Scientific summary

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Scientific summary

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Background

The National Institute for Health and Care Excellence (NICE), NHS England and NHS Improvement are currently undertaking a project to assess the feasibility of innovative models that pay for antimicrobials (AMs) based on an evaluation of their value to the NHS as opposed to the volumes used. This project involves evaluation of two AMs to inform commercial discussions regarding contract value for a period of up to 10 years. This report details the evaluation phase of this project for cefiderocol (Fetcroja), which is manufactured by Shionogi. Cefiderocol is an injectable siderophore cephalosporin and received a marketing authorisation in April 2020 for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Aim and objectives

The aim of this evaluation is to assess the value of cefiderocol to the NHS in England when used within its licensed indications.

Specific objectives are:

1. To identify two high-value clinical scenarios (HVCSs), within its broad licensed indications, for which cefiderocol is expected to have a significant impact on patients' outcomes in terms of reducing mortality risks and improving health-related quality of life (HRQoL).
2. To undertake an 'evidence mapping' exercise and relevant systematic literature reviews to characterise the available clinical effectiveness evidence for the use of cefiderocol in the HVCSs.
3. To establish an appropriate decision-analytic model to quantify the costs and health benefits of the use of cefiderocol under various usage scenarios compared with usage scenarios involving other available AMs in the HVCSs. The decision-analytic model was required to estimate costs and health effects at both the individual level and the aggregate population level, providing population-level incremental net health effects (INHEs).
4. Drawing on the systematic reviews and evidence synthesis, national-level data on healthcare-associated infections and other sources as needed, to identify evidence to populate the decision-analytic models.
5. To use structured expert elicitation as necessary to supplement the available evidence to populate the decision-analytic models.
6. To use available evidence and, where necessary, expert opinion quantitatively to extrapolate estimated population-level INHEs associated with cefiderocol in the HVCSs to other expected uses for the product within the product's licensed indications.

Expected usage and high-value clinical scenarios

The licensed indication for cefiderocol is broad. In practice, to control the spread of resistance to cefiderocol and to preserve its long-term viability as an effective treatment option against highly resistant pathogens, cefiderocol may be used in a more restricted group of patients than permitted by its

license. Quantifying the health and cost implications of using cefiderocol across anticipated NHS usage, even within this restricted population, remains challenging, as the use is expected in infections which differ in causative organism (pathogen, resistance mechanism), site of the infection, healthcare setting and other patient characteristics.

This evaluation characterises the value of cefiderocol across its range of expected uses via a two-step approach. First, decision modelling is used quantitatively to assess the value of cefiderocol in a set of scenarios defined by features of the pathogen, site of infection, healthcare setting and other patient characteristics, considered to represent important uses of cefiderocol; referred to as the HVCSs. Second, rescaling is used to estimate how this evidence can be used to provide quantitative assessments of value in the overall population expected to receive cefiderocol, including patients who fall outside the HVCSs but who are relevant to determining the overall value of cefiderocol to the English NHS.

The HVCSs were selected to reflect areas of clinical use where there is a current significant burden from resistant infections, and cefiderocol is expected to offer significant improvements over existing treatments in terms of efficacy and/or safety. The HVCSs were selected based on feedback from the manufacturer, clinical advisors to the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU) and broader stakeholders involved in the NICE scoping process. The HVCSs focus on the following patient populations:

1. Empiric setting (ES): patients with an infection strongly suspected to be caused by metallo-beta-lactamase (MBL)-producing *Enterobacterales* or MBL-producing *Pseudomonas aeruginosa* in patients with hospital-acquired pneumonia or ventilator-associated pneumonia (HAP/VAP). In this patient group, the pathogen, resistance mechanism and antibiotic susceptibility have not yet been established, but treatment is initiated immediately due to the severity of the infection.
2. Microbiology-directed setting (MDS): patients with an infection confirmed to be caused by MBL *Enterobacterales* or MBL *P. aeruginosa*, where antibiotic susceptibility testing results are available, and where the site of infection is HAP/VAP or complicated urinary tract infection (cUTI).

The resourcing for this project was equivalent to that of a diagnostic assessment review or multiple technology assessment for NICE, but the levels of analysis extend from the typical focus of those evaluations on a single type of patient for one indication and setting. In this evaluation, we also include population-level health effects now and over time, and across several indications and settings. The objective is to use appropriate analyses of the available evidence at every level, but the detail in those analyses is inevitably constrained by the time and resources available for the project.

Clinical evidence

Methods

There are evidential challenges when evaluating the use of new or nearly new AMs to treat infections caused by multidrug-resistant (MDR) pathogens. Randomised controlled trials (RCTs) are of generally low relevance as they tend not to recruit patients with MDR pathogens. Therefore, relative treatment effects between the intervention and comparator cannot be generalised to MDR pathogens, as this may overestimate the efficacy of the comparator.

It was anticipated that RCTs were unlikely to be the primary source of evidence. Therefore, a mapping review was undertaken to establish available evidence and ascertain which approach to estimating comparative effectiveness could inform an economic model. Reviews 1 and 2 considered RCTs and observational studies of cefiderocol in patients with HAP/VAP or cUTI infections caused by MBL *Enterobacterales* or *P. aeruginosa* or suspected to be caused by carbapenem-resistant *Enterobacterales* or *P. aeruginosa*. In Review 3, in vitro susceptibility studies were considered. These studies provide evidence on the proportion of isolates that are susceptible to treatments and comparators as an indication of

relative efficacy. Susceptibility studies were considered eligible if they reported susceptibility for MBL *Enterobacterales* or *P. aeruginosa* isolates, from any infection site (clinical advisors indicated that infection site was not associated with susceptibility profile), and reported susceptibility to cefiderocol and at least one comparator as defined by the HVCSs (colistin, meropenem, tigecycline, aztreonam, fosfomycin, gentamicin, amikacin, tobramycin).

Susceptibility studies test isolates in vitro to ascertain the minimum concentration of any given treatment that is needed to inhibit growth of the microbe [the minimum inhibitory concentration (MIC)]. If this is below the clinical breakpoint published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [or by the Clinical Laboratory Standards Institute (CLSI) from the USA], the isolate is considered susceptible, and is likely to respond to treatment in vivo. In the UK, the British Society for Antimicrobial Chemotherapy (BSAC) recommends use of EUCAST guidelines.

Systematic searches across relevant databases [MEDLINE, EMBASE and Centre for Review and Dissemination (CRD) database] were conducted in March 2021. EEPRU also considered evidence submitted by Shionogi and Public Health England (PHE). After mapping, only Review 3 was pursued, since there was insufficient evidence from Reviews 1 and 2. Risk of bias assessment was performed using a bespoke tool developed for this evaluation. No studies of fosfomycin were identified. An additional rapid review was conducted to identify studies reporting the susceptibility of fosfomycin and at least one other HVCS comparator.

A random-effects network meta-analysis (NMA) of susceptibility studies was conducted to allow a comprehensive synthesis of evidence on all relevant treatments. A different network was constructed for each subgroup of pathogens (MBL *Enterobacterales* and MBL *P. aeruginosa*), since susceptibility profiles were expected to differ. For each of these, a network was constructed using EUCAST breakpoints and another using CLSI breakpoints. The EUCAST networks were considered the main analysis, while the CLSI networks were considered in sensitivity analyses. Sensitivity analyses were also conducted to test assumptions around the inclusion of comparators in the network, to assess the impact of missed data on the analysis, and prioritising PHE data where possible as these are from English isolates and, therefore, have the highest relevance.

Two additional reviews were conducted to provide evidence on the link between susceptibility and clinical outcomes (Review 4) and between susceptibility and long-term outcomes (Review 5) in the sites of interest. A further review (Review 6) was conducted to identify any important safety implications of cefiderocol.

Results

The reviews of RCT and observational studies identified insufficient evidence to inform an assessment of clinical effectiveness. One RCT did report subgroup data relating to MBLs, but the subgroup was small (n = 16 in the cefiderocol arm, n = 7 in the best available therapy arm) and was, therefore, not used due to the chance of baseline imbalances introducing bias. The key limitations of the observational studies that were identified included small numbers of MBL infections (range n = 2–17 patients), high levels of heterogeneity with respect to prognostic factors, and data not being reported for the sites of interest.

Review 3 identified in vitro susceptibility studies in relatively large samples of MBL *Enterobacterales* or *P. aeruginosa* isolates obtained from a range of clinical sites of infection. Three studies (SIDERO CR, SIDERO WT and Johnston *et al.*) reporting data for cefiderocol and at least one comparator met the inclusion criteria and were synthesised. The separate review of fosfomycin identified 10 studies.

In the MBL *Enterobacterales* EUCAST analysis, cefiderocol was associated with a lower susceptibility relative to colistin [odds ratio (OR) 0.32, 95% credible intervals (CrI) 0.04 to 2.47], but the result was not statistically significant. Fosfomycin had a similar OR (OR 0.34, 95% CrI 0.06 to 1.96) compared to

colistin as cefiderocol. The remainder of the treatments were also associated with lower susceptibility than colistin, but the results were not statistically significant. In the MBL *P. aeruginosa* EUCAST analysis, cefiderocol was associated with a lower susceptibility relative to colistin (OR 0.44, 95% CrI 0.03 to 3.94), but the result was not statistically significant. The remainder of the treatments were associated with no susceptibility. Heterogeneity was high in both networks.

In the sensitivity analyses using CLSI breakpoints, where the breakpoint for cefiderocol is higher, cefiderocol was associated with a higher susceptibility relative to colistin. However, the results were very uncertain in some of the NMAs due to sparse data and a large number of treatment arms with either zero or 100% susceptibility.

Review 4 (link between susceptibility and clinical outcomes) identified two studies that reported mortality or hospital length of stay (LoS) conditional on susceptibility to empiric treatment and were selected for use in the model for the ES. No useful evidence relating to the MDS was identified. Review 5 (link between susceptibility and *long-term* clinical outcomes) did not identify any relevant literature, but an unpublished study (CARBAR) was submitted by Shionogi that contained useful data. Review 6 indicated that cefiderocol does not appear to increase the risk of acute kidney injury (AKI), *Clostridium difficile*, or any other serious adverse events, compared to non-toxic comparators (i.e. comparators other than colistin or an aminoglycoside). No study reported a comparison of cefiderocol exclusively to colistin or aminoglycosides. Event rates were generally very low or zero.

Discussion of clinical evidence: There were limitations to the approach selected and analyses done. Key limitations include: susceptibility could be considered, at best, a surrogate outcome, but no pre-specified criteria for judging the suitability of the surrogate or the linking evidence were applied; linking data were limited and not specific to the pathogen-mechanism combination, and expert elicitation had to be relied upon to evidence the link in the MDS; uncertainties relating to the determination and application of breakpoints; and the NMAs results were associated with high levels of heterogeneity.

Economic evidence

Methods

No published existing economic evaluations assessed the use of cefiderocol in the HVCSs or areas of expected usage. The manufacturer did not submit a cost-effectiveness model.

A de novo decision-analytic model was developed to predict the cost and health consequences of introducing cefiderocol within the HVCSs. These were summarised as INHEs. These are estimates of the quality-adjusted life-years (QALYs) associated with introducing cefiderocol if it was supplied free of charge to the NHS, taking in to account both its health benefits and the health benefits of freeing up NHS resources (e.g. via reduced time in hospital) calculated using an estimate of health opportunity cost of £20,000/QALY. This means that for every £20,000 saved, 1 QALY of health can be generated within the NHS. The estimates of INHE will be used in subsequent negotiations to determine an appropriate payment level for cefiderocol.

This quantitative analysis comprises three components: an assessment of the INHEs of introducing cefiderocol within the HVCSs at the patient level; an assessment of INHEs within the HVCSs at the population level; and an assessment of how population-level INHEs within the HVCSs might appropriately be rescaled to reflect expected usage across the English NHS.

The patient-level component is structured similarly to decision models developed as part of other NICE processes and characterises the cost, mortality and morbidity consequences of introducing cefiderocol over a patient's lifetime. Separate but related models are developed for the ES and MDS. In the ES, empiric treatment with cefiderocol is compared to: empiric treatment with a non-colistin/

aminoglycoside-based treatment (MBL *P. aeruginosa* only); empiric treatment with colistin/aminoglycoside-based treatment (considered more toxic). In the MDS, we compare outcomes in the overall microbiology-directed cohort who receive tailored therapy with cefiderocol available as a treatment option, to outcomes when this cohort receive tailored therapy with existing AMs only.

In the ES, patients are suspected to have a MDR infection, so it is necessary to model outcomes for both patients in whom this suspicion is confirmed and for those in whom this suspicion turns out to be incorrect. The probability of having the suspected pathogen/resistance mechanism is informed by Second-Generation Surveillance System (SGSS) national surveillance data supplied by PHE for this evaluation. The key driver of effectiveness is in vitro susceptibility as estimated via the evidence syntheses discussed above. Higher susceptibility reduces mortality and LoS in hospital. These relationships are based on a combination of evidence from the literature and structured expert elicitation. Colistin or aminoglycoside-based therapy is expected to be associated with higher rates of AKI than other agents (including cefiderocol), which has significant consequences for patients' short- and long-term mortality, morbidity and costs. Safety differences between colistin or aminoglycoside-based therapy and other agents are, therefore, modelled using evidence from published systematic reviews. Lifetime costs, quality of life and mortality were predicted accounting for the highly comorbid nature of the patient population and the increased risk of chronic kidney disease (CKD) resulting from AKI.

The population-level component uses a forecast-based approach to aggregate the patient-level predictions to the population level accounting for the size of, and growth over time in, the eligible patient population in England within each HVCS. This component also reflects how resistance is likely to develop to cefiderocol and existing AMs over time. Predictions of population-level INHE are presented for patients initiated on treatment over the next 20 years. Current numbers of patients within the HVCSs were based on evidence from SGSS. Future growth in the number of patients in the HVCSs was based on statistical forecasting models fitted to time-series data from a national reference laboratory data set supplied by PHE for this evaluation. A series of scenarios reflects the potential emergence of resistance to cefiderocol. We did not model changes in resistance to existing AMs over time due to the sparsity of evidence available to inform these forecasts.

Predicted overall population-level INHEs corresponding to the expected use of cefiderocol in the English NHS were generated by rescaling the population-level INHEs from the HVCSs to reflect additional areas of expected usage. These included patients with bloodstream and intra-abdominal infections (BSIs and IAIs) known or suspected to be caused by MBL *Enterobacterales* or MBL *P. aeruginosa*, and patients with infections caused by *Stenotrophomonas* across a range of sites (HAP/VAP, cUTI, BSIs and IAIs). This rescaling was based on population size estimates from SGSS and the use of expert opinion to inform the similarity in patient-level INHEs between the patients falling within the HVCSs and these additional sites and pathogens of interest.

The literature on the economic evaluation of AMs has described a range of elements of value associated with these products that are not relevant to evaluations of other healthcare interventions. We also, therefore, summarise the extent to which these elements of value are captured within the quantitative estimates and, where this has not been possible, whether they are likely to substantively modify the quantitative estimates of value presented.

Results

Patient-level INHEs in the HVCS

For HAP/VAP patients treated empirically, the base-case INHEs (0.15 QALYs) are similar in patients with suspected MBL *Enterobacterales*, and those with suspected *P. aeruginosa*. The results were very sensitive to the proportion of patients who have MBL *Enterobacterales*, use of the CLSI breakpoints, AKI risk, AKI-related mortality and long-term survival (range across scenarios: 0.00–0.23 QALYs).

For patients treated in the MDS, the base-case INHEs associated with cefiderocol are much higher for MBL *P. aeruginosa* (0.15 QALYs for HAP/VAP and cUTI) than MBL *Enterobacterales* (0.02 QALYs for HAP/VAP and cUTI) as the latter patient group has a higher probability of being susceptible to a non-colistin/aminoglycoside-based treatment, and hence not requiring treatment with cefiderocol. There is a large degree of uncertainty in the patient-level INHE in the MBL *P. aeruginosa* population (range across scenarios 0.01–0.25). This reflects uncertainties in the susceptibility to non-colistin/aminoglycoside-based treatments. Results in the MBL *P. aeruginosa* populations are subject to additional uncertainty due to limitations in the evidence base for the comparators (fosfomycin plus meropenem and fosfomycin plus colistin), as fosfomycin does not have an established breakpoint for *P. aeruginosa*, making links to clinical outcomes more tenuous. Furthermore, the available evidence to inform the relative susceptibility of fosfomycin was based on very small studies (n = 7 in the EUCAST and n = 20 in the CLSI networks).

We were unable to select a base case for the population-level results. Population-level results are, therefore, presented for two different approaches to estimating infection numbers (based on different methods to classify infections from clinical specimen sites); two alternative approaches to forecasting increases in infections over time (based on whether observed trends are assumed to persist indefinitely or not); and three different trajectories with respect to resistance emergence to cefiderocol (1%, 5% and 10% at 20 years).

Across these scenarios, population-level INHEs range from 896 to 3559 QALYs. The results are particularly sensitive to the assumption about which clinical specimen sites are indicative of HAP/VAP. A substantial part of the value of cefiderocol (20 to 38% depending on scenario) is generated among patients with *Stenotrophomonas* who were outside of the HVCSs considered by EEPRU. Departures from the base-case assumptions in the patient-level model also had substantial effects on the mean population-level INHEs. The population size estimates used to generate the estimates of population-level INHEs are subject to additional uncertainties relating to the completeness of the national data, whether all tested patients would fall within the HVCS population for empiric treatment, the potential double counting of samples from the same infectious episode and inherent uncertainties in forecasting population size over time.

In addition, estimates of population-level INHEs were generated using a number of strong assumptions about how evidence can be generalised between settings. Namely, that patient-level INHE of cefiderocol in patients with BSI can be approximated based on outcomes in HAP/VAP patients, and that the patient-level INHE of cefiderocol in patients with IAI can be proxied by that in patients with cUTI. These assumptions were based on discussions with clinical experts.

Based on the available evidence, we concluded that diversity value, transmission value and spectrum value were unlikely to be significant drivers of population-level INHEs for cefiderocol. Insurance value was captured for the HVCS, though the benefits of cefiderocol use in novel future outbreaks were not captured and remain highly uncertain. EEPRU considers that it is possible that cefiderocol use will facilitate additional or at least more prompt receipt of required treatments/procedures for certain groups but that the magnitude of these enablement benefits remains highly uncertain.

Conclusion

The quantitative assessment of value in this report indicates that cefiderocol is associated with a base-case population-level INHE across its areas of expected usage of 896 to 3559 QALYs over 20 years. These quantitative assessments of value were informed by a series of interlinked decision-analytic models informed by evidence collated via systematic reviews of the literature and evidence synthesis, additional national data provided by PHE, structured expert elicitation and, where necessary, assumptions informed by clinical opinion.

This work has provided quantitative estimates of the value of cefiderocol within its areas of expected usage within the NHS. The results indicate that the maximum amount the NHS could pay for cefiderocol was £18 million to £71 million if the health lost as a result of making these payments rather than funding other NHS services is not to exceed the health benefits of using cefiderocol. The high level of uncertainty could be addressed via further research; however, the appropriateness of amending payments to reflect revised estimates of value requires further consideration.

A broader and important question is 'what would represent the 'optimal' scope of usage for cefiderocol?' Further methodological and quantitative work is required to address this question.

Study registration

No registration of this study was undertaken.

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