**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Antimicrobial Health Technology Evaluation**

Cefiderocol for treating severe aerobic Gram-negative bacterial infections

Final scope

# Evaluation objective

To assess the value of cefiderocol to the NHS in England for treating severe aerobic Gram-negative bacterial infections.

# The project

This health technology evaluation is part of a project to test new payment models for antimicrobials. The payment discussions between NHS England & NHS Improvement and the manufacturer of cefiderocol will be informed by this evaluation. These payments will be based on the value of cefiderocol to the NHS in England, and not linked to the volumes sold. The approach to value assessment is set out in the 2018 EEPRU report1 and in the [Evaluation Framework](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf). If the discussion between NHS England & NHS Improvement and the manufacturer is successful, they will enter into a 3-year contract, with an option to extend for up to another 7 years, during which the manufacturer will receive an annual, value-based payment.

# Background

Antimicrobial resistance develops when microorganisms, like bacteria and fungi, adapt and become immune to the drugs designed to treat them.2 Multidrug-resistant bacteria can spread rapidly within both hospitals and community settings, further contributing to heightened resistance and antimicrobial use.3 Antimicrobial stewardship guidelines aim to change prescribing practice to help slow the emergence of antimicrobial resistance and ensure that antimicrobials remain an effective treatment for infection.

The World Health Organisation (WHO) maintains [a list of priority pathogens](https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed) where, due to the development of resistance, new antimicrobials are urgently needed. The pathogens that the WHO deems ‘critical’ priorities are:

* carbapenem-resistant Acinetobacter baumannii
* carbapenem-resistant Pseudomonas aeruginosa
* carbapenem-resistant, extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (including: Klebsiella pneumonia, Escherichia coli, and species of Enterobacter, Serratia, Proteus, Providencia and Morganella).

These pathogens are multidrug-resistant Gram-negative bacteria that can cause severe infections in secondary care settings, such as pneumonia and bloodstream infections (bacteraemia), that can often be fatal.4,5

In secondary care settings, Public Health England and NICE guidance recommend prescribing according to the ‘Start Smart, Then Focus’ algorithm. For severe and life-threatening infections, this means initiating treatment with an effective antimicrobial within 1 hour of diagnosis and obtaining cultures prior to starting therapy if possible. Then at clinical review (48-72 hours later) microbiology should lead to a decision either: (1) to stop treatment, (2) switch to oral antimicrobials, (3) change to other antimicrobials, (4) continue treatment, or (5) switch to outpatient parenteral antibiotic therapy (OPAT).

# The technology

Cefiderocol (Fetcroja, Shionogi) is a siderophore cephalosporin that binds to penicillin binding proteins, inhibiting bacterial peptidoglycan cell wall synthesis and causing cell lysis and death. It is given intraveneously.

Cefiderocol received a marketing authorisation in April 2020 for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options.

It has been studied in clinical trials compared with either dual therapy imipenem and cilastatin, meropenem or ‘best alternative treatment’ in hospitalised adults with serious infections caused by gram-negative bacteria. Two of the trials included people in whom multi-drug resistant infection was suspected, and one trial included people only if carbapenem-resistance had been confirmed. The following types of infection were included in the studies:

* complicated urinary tract infections
* hospital-acquired pneumonia
* ventilator-associated pneumonia
* healthcare-associated pneumonia
* sepsis and bacteraemia.

In vitro studies suggested that cefiderocol might be efficacious against Achromobacter species, Acinetobacter baumannii complex, Burkholderia cepacia complex, Citrobacter freundii complex, Citrobacter koseri, Escherichia coli, Enterobacter cloacae complex, Klebsiella (Enterobacter) aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Serratia species, Pseudomonas aeruginosa, Serratia marcescens and Stenotrophomonas maltophilia.

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| **Intervention(s)** | Cefiderocol |
| **Population(s)** | People receiving treatment in secondary or tertiary care settings in whom resistant aerobic Gram-negative infection is suspected/confirmed, with limited treatment options. |
| **Comparators** | Clinical management without cefiderocol |
| **Outcomes** | The outcome measures to be considered include:* All-cause mortality
* Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy was needed)
* Microbiologic eradication
* Emergence of resistance
* Hospital days
* Intensive care unit (ICU) days
* Readmission rate within 90 days of treatment
* Number of treatment days
* Health-related quality of life
* Adverse events (including those associated with Clostridium Difficile infection and renal toxicity)
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| **Economic analysis** | The NICE guide to the methods for technology appraisals (2013) will be followed where possible, with the following adaptations. The aim of the analysis will be to estimate the value of cefiderocol to the NHS expressed under the stewardship scenario(s) that is(are) expected to generate the highest net health benefits to the NHS.Within the timescale and resources assigned, it is unlikely to be possible to undertake detailed economic modelling for all pathogens/clinical syndrome combinations. The evaluation will include one or more high value clinical scenarios for detailed study, together with additional indications that need to be considered but where bespoke economic models will not be developed. For these additional indications a summary of relevant clinical and health economic information will be provided. Estimates of value to the NHS in England need to take account of the high value clinical scenarios and additional indications.The economic analysis outputs will be, wherever feasible, expressed in population net health benefits as measured in quality-adjusted life years. Population net health benefit should be estimated over the full time horizon of the economic model and options presented for assigning an appropriate proportion of the total value to a potential 10-year contract period.In the base-case analysis a threshold of £20,000 per quality-adjusted life year should be used for the calculation of net health benefits.For antimicrobials, the evaluation will include consideration of additional elements of value as set out in the [Evaluation Framework](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf). These include spectrum value, transmission value, enablement value, diversity value, and insurance value. Depending on available evidence, several stewardship strategies may be modelled and compared (e.g. reserving cefiderocol until testing reveals specific resistance patterns, selected empiric use in high-risk settings, rotation of antimicrobials) to identify the optimal usage scenario. |
| **Other considerations**  | Guidance will include consideration of the optimal stewardship scenarios. |
| **Related NICE recommendations and NICE Pathways** | **Related Guidelines:** [Pneumonia (hospital-acquired): antimicrobial prescribing](https://www.nice.org.uk/guidance/ng139/chapter/Update-information) (2019) NICE guideline 139. No review date.[Pyelonephritis (acute): antimicrobial prescribing](https://www.nice.org.uk/guidance/ng111) (2018) NICE guideline 111. No review date.[Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](https://www.nice.org.uk/guidance/ng15) (2015) NICE guideline 15. No review date.[COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital](https://www.nice.org.uk/guidance/ng173). NICE guidline 173 (2020). No review date.**Related Quality Standards:**[Antimicrobial stewardship](https://www.nice.org.uk/guidance/qs121) (2016) NICE quality standard 121**Related NICE evidence summaries:**[Antimicrobial prescribing: cefiderocol](https://www.nice.org.uk/advice/es31/chapter/Product-overview) (2020) NICE evidence summary 31 |
| **Related National Policy**  | The NHS Long Term Plan, 2019. [NHS Long Term Plan](https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/)[UK 20-year vision for antimicrobial resistance](https://www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance) (2019)[UK 5-year action plan for antimicrobial resistance 2019 to 2024](https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024) (2019)[Antimicrobial resistance](https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources) (updated 2019)[Antimicrobial Resistance: resource handbook](https://www.gov.uk/government/publications/antimicrobial-resistance-resource-handbook) (updated 2017)[Antimicrobial stewardship: Start Smart, Then Focus](https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus) (updated 2015) |

# References

1 Rothery C et al. (2018) [Framework for Value Assessment of New Antimicrobials. Implications of alternative funding arrangements for NICE Appraisal](http://www.eepru.org.uk/article/framework-for-value-assessment-of-new-antimicrobials-implications-of-alternative-funding-arrangements-for-nice-appraisal/). Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. EEPRU Research Report 059

2 Wells V et al. (2017) ‘Implementing WHO, EU and UK AMR Strategies and Action Plans: Has the World Lived up to the Challenge?’, The Lancet Infectious Diseases.

3 Cliodna AM McNulty et al. (2007) ‘Don’t Wear Me out—the Public’s Knowledge of and Attitudes to Antibiotic Use’, Journal of Antimicrobial Chemotherapy

4 World Health Organisation (2017) ‘WHO publishes list of bacteria for which new antibiotics are urgently needed’ via <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed> (accessed 8 December 2020)

5 World Health Organisation (2017) Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. World Health Organisation, Geneva, Switzerland. Report via <https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1> (accessed 10 December 2020)