NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Antimicrobial Health Technology Evaluation

Ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections

Draft scope

Draft evaluation objective

To assess the value of ceftazidime with avibactam to the NHS in England for the treatment of 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 ceftazidime with avibactam will be informed by this evaluation. These payments will be based on the value of ceftazidime with avibactam to the NHS in England, and not linked to the volumes sold. The approach to value assessment is set out in the 2018 EEPRU report[1] and in the Evaluation Framework. 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 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 IV antimicrobial, (4) continue treatment, or (5) switch to outpatient parenteral antibiotic therapy (OPAT).

The technology

Ceftazidime with avibactam (Zavicefta, Pfizer Limited) has a marketing authorisation for treating:

- complicated intra-abdominal infections
- complicated urinary tract infections, including pyelonephritis
- hospital-acquired pneumonia, including ventilator-associated pneumonia
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above
- infections caused by aerobic gram-negative organisms with limited treatment options.

It can be used in adults and children aged 3 months and older.

Ceftazidime with avibactam received marketing authorisation in June 2016 and is a combination antimicrobial consisting of a third-generation cephalosporin (ceftazidime) and a non-beta-lactam, beta-lactamase inhibitor (avibactam). Ceftazidime with avibactam is administered by intravenous infusion.

Ceftazidime with avibactam has been studied in several clinical trials, compared with either carbapenems or 'best available' antimicrobial treatment (colistin-based or non-colistin-based) in adults with hospital-acquired pneumonia, ventilator-associated and healthcare-associated pneumonia, bloodstream infection or sepsis, or complicated urinary tract infection due to carbapenem-resistant gram-negative bacteria. Efficacy has been demonstrated in clinical studies against the following pathogens: Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, and Serratia marcescens. In vitro studies have suggested that ceftazidime with avibactam might also be efficacious against Citrobacter koseri, Enterobacter aerogenes, Morganella morganii, Proteus vulgaris and Providencia rettgeri.

Intervention(s)	Ceftazidime with avibactam
Population(s)	People receiving treatment in secondary or tertiary care settings in whom resistant gram-negative infection is suspected/confirmed, with: • complicated intra-abdominal infections • complicated urinary tract infections, including pyelonephritis • hospital-acquired pneumonia, including ventilator-associated pneumonia • infections caused by aerobic gram-negative bacteria in adults with limited treatment options • bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Comparators	Clinical management without ceftazidime with avibactam, which may include: • cefiderocol • ceftolozane with tazobactam • colistimethate sodium (colistin), alone or in combination with fosfomycin or meropenem • ertapenem • gentamicin, alone or in combination with meropenem • imipenem with cilastatin • imipenem with cilastatin and relebactam • meropenem • meropenem with vaborbactam • piperacillin with tazobactam • tigecycline • tobramycin, alone or in combination with meropenem

Outcomes	The outcome measures to be considered include: • All-cause mortality • 90-day 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 • Health-related quality of life • Adverse events.

Economic analysis	The NICE guide to the methods for technology appraisal (2013) will be followed where possible, with the following adaptations. The aim of the analysis will be to estimate the value of ceftazidime with avibactam to the NHS under the stewardship scenario that is expected to generate the highest net health benefit 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 "primary" indications 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 primary 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. These include diversity value, transmission value, enablement value, spectrum value, and insurance value. Several stewardship strategies might need to be modelled and compared (e.g. rotation of antimicrobials, mixing protocols, reserving ceftazidime with avibactam until testing reveals specific resistance patterns) 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 (2019) NICE guideline 139. No review date. Pyelonephritis (acute): antimicrobial prescribing (2018) NICE guideline 111. No review date.

	Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline 15. No review date. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital. NICE guidline 173 (2020). No review date. **Related Quality Standards:** Antimicrobial stewardship (2016) NICE quality standard 121 **Related NICE evidence summaries:** Antimicrobial prescribing: Ceftazidime/avibactam (2017) NICE evidence summary 16
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan UK 20-year vision for antimicrobial resistance (2019) UK 5-year action plan for antimicrobial resistance 2019 to 2024 (2019) Antimicrobial resistance (updated 2019) Antimicrobial Resistance: resource handbook (updated 2017) Antimicrobial stewardship: Start Smart, Then Focus (updated 2015)

Questions for consultation

1. Does the population reflect those that would be eligible to receive ceftazidime with avibactam in the NHS in England?
    a. The marketing authorisation for ceftazidime with avibactam includes people 'with limited treatment options'. How is 'limited treatment options' defined in practice? Does it refer to severe infections where resistance is suspected/confirmed, or is there a differentiation between the two terms?

2. Which treatments are considered to be established clinical practice in the NHS for people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?

3. Do established treatments differ according to infection site in people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?

4. What criteria should be used to identify the primary indication(s) for the economic analysis?
    a. For example: unmet need, disease severity, absolute patient numbers, availability of alternative treatment(s). Are there any others?

    For an explanation of the "primary" indication(s), please refer to the 'economic analysis' section of the table above, and paragraphs 4.3 and 4.4 of the Evaluation Framework.

5. In which indication(s) is ceftazidime with avibactam expected to have the highest value when considering the criteria listed under question 4.a?
    a. What are the most important comparators for this indication(s)?

6. What testing strategies are used in clinical practice for people with severe infections due to aerobic gram-negative bacteria where resistance is suspected?

7. Are the outcomes listed appropriate?

8. What stewardship scenarios are relevant to be considered in the analysis?

9. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed evaluation and scope may need changing in order to meet these aims. In particular, please tell us if the proposed evaluation and scope:

    - could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ceftazidime with avibactam is licensed;

    - could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

    - could have any adverse impact on people with a particular disability or disabilities.

    Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

10. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

References

[1] Rothery C et al. (2018) 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)