Ceftazidime with avibactam 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

Background

This evaluation is one of two performed as part of a pilot conducted by the National Institute for Health and Care Excellence (NICE), NHS England (NHSE) and NHS Improvement 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. These projects informed commercial discussions regarding contract value for a period of up to 10 years.

This report details the evaluation phase for ceftazidime with avibactam (CAZ-AVI, brand name Avycaz), a fixed-dose combination medication composed of ceftazidime, a cephalosporin antibiotic, and avibactam, a beta-lactamase inhibitor manufactured by Pfizer which received a marketing authorisation in June 2016 for treatment in adults and paediatric patients (> 3 months) for complicated intra-abdominal infections (cIAI), complicated UTI (cUTI), hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP), bacteraemia (adults only) associated with the aforementioned infections and treatment of infections caused by aerobic Gram-negative organisms with limited treatment options.

Aim and objectives

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

Specific objectives are:

1. To identify two high-value clinical scenarios (HVCSs) for which CAZ-AVI is expected to impact on mortality risks and improve health-related quality of life
2. To undertake an 'evidence mapping' exercise and relevant systematic literature reviews to characterise the available clinical effectiveness evidence for the use of CAZ-AVI in the HVCSs.
3. To establish an appropriate decision-analytic model to quantify the costs and health benefits of the use of CAZ-AVI 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 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, 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 to quantitatively extrapolate estimated population INHEs associated with CAZ-AVI in the HVCSs to other expected uses for the product within the product's licensed indications.

Expected usage and high-value clinical scenarios

To control the spread of resistance to CAZ-AVI and to preserve its long-term viability as an effective treatment option against highly resistant pathogens, CAZ-AVI was expected to be used in a narrower group of patients than permitted by its license. This evaluation characterised the value of CAZ-AVI in two steps. First, decision modelling assessed quantitatively the value of CAZ-AVI in a set of

'high-value clinical scenarios' (HVCSs). Secondly, rescaling was used to provide a quantitative assessment of value in the overall population expected to receive CAZ-AVI in the English NHS, including scenarios outside the HVCSs.

The HVCSs were scenarios where there was currently significant burden from resistant infections, and where CAZ-AVI was expected to offer significant improvements over existing treatments in terms of efficacy and/or safety. The HVCSs focus on the following patient populations:

1. Empiric setting (ES): infections strongly suspected to be caused by oxacillinase-48 (OXA-48) Enterobacterales in patients with hospital-acquired pneumonia or ventilator-associated pneumonia (HAP/VAP). 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 OXA-48 Enterobacterales, where antibiotic susceptibility testing results were available, and where the site of infection was HAP/VAP or 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 beyond the typical focus of those evaluations, to include population-level health effects now and over time, as well as across several indications and settings. The analyses are inevitably constrained by the time and resources available for the project.

Clinical evidence

Methods

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 in patients with HAP/VAP or cUTI infections caused by OXA-48 Enterobacterales or suspected to be caused by carbapenem-resistant Enterobacterales. In Review 3 in vitro susceptibility studies of OXA-48 Enterobacterales isolates which reported the proportion of isolates from any infection site that were susceptible to the HVCS treatment and at least one relevant comparator (colistin, meropenem, tigecycline, aztreonam, fosfomycin, gentamicin, amikacin, tobramycin) were sought.

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 Pfizer and Public Health England (PHE).

After mapping, only Review 3 was pursued, since there was insufficient evidence from Reviews 1 and 2 (see details in Results below). Risk-of-bias assessment was performed using a bespoke tool developed for this evaluation.

A random-effects NMA of susceptibility studies was conducted. Subgroup and sensitivity analyses were planned to investigate the impact of clinical sources of heterogeneity including: inclusion criteria (use of resistance to a comparator to select study sample); co-carriage of MBLs; the proportion who were carbapenem-sensitive; whether the sample was recruited consecutively; and what laboratory methods and breakpoints were used to assess susceptibility.

Review 4 aimed to provide evidence on the link between susceptibility and clinical outcomes and Review 5 between susceptibility and long-term outcomes in the sites of interest. Review 6 aimed to assess the safety of CAZ-AVI.

Results

The mapping reviews of RCT and observational studies identified insufficient evidence to inform an assessment of clinical effectiveness since the RCTs included very small numbers of OXA-48 Enterobacterales infections and did not report these data as a subgroup analysis and the observational data were not reported separately for the sites of interest (cUTI and HAP/VAP), the studies were small and highly heterogeneous with respect to prognostic factors, and individual patient data (IPD) were not available within the timeframe of this evaluation.

In the review of susceptibility studies, 28 data sources met the initial inclusion criteria. One, from PHE, which included isolates submitted voluntarily to the antimicrobial resistance and healthcare-associated infections (AMRHAI) reference laboratory, had high relevance, but several limitations. EEPRU therefore included a broader set of evidence synthesised using network meta-analysis (NMA). Sixteen studies and data sources met the inclusion criteria. In the synthesis, CAZ-AVI was associated with a statistically significantly higher susceptibility relative to colistin [odds ratio (OR) 7.24, 95% credible interval (CrI) 2.58 to 20.94]. The remainder of the treatments were associated with lower susceptibility than colistin (OR < 1). Heterogeneity was extremely high [standard deviation (SD) 1.56, 95% CrI 1.28 to 1.93] and sensitivity analyses were conducted to investigate the sources of heterogeneity.

The evidence network using EUCAST methods and breakpoints to assess susceptibility was selected as the base-case analysis to inform the economic evaluation since heterogeneity was lower and there was a clinical rationale to support restricting to studies that had used EUCAST laboratory methods and breakpoints as these are more commonly used in England. A scenario analysis was planned to include the result from the full analysis set. A further scenario was planned restricted to studies with no-MBLs and that had used EUCAST laboratory methods and breakpoints, which left one study (Vazquez-Ucha *et al.*). A further scenario analysis was planned using the PHE data alone, due to its high relevance to the evaluation.

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

Discussion of clinical evidence: there were some limitations to the approach selected and analyses done. Key limitations include: susceptibility could be considered, at best, a surrogate outcome; 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 NMA results were associated with high levels of heterogeneity.

Economic evidence

Methods

No published existing economic evaluations that assessed the use of CAZ-AVI in the HVCSs or areas of expected usage were identified. The manufacturer's cost-effectiveness model estimated that introduction of CAZ-AVI was associated with an expected INHE benefit of approximately 20,000 quality-adjusted life-years (QALYs) over a 10-year time horizon, based on a cost-effectiveness threshold of £30,000 per QALY. EEPRU considered the model to contain several strong assumptions and it

assumed a much broader population of patients would receive CAZ-AVI than considered appropriate by clinical advisors to EEPRU.

Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions developed a de novo decision-analytic model to predict the cost and health consequences (summarised as population-level INHEs) of introducing CAZ-AVI within the HVCSs. These estimates assumed CAZ-AVI was supplied free of charge to the NHS, and use an estimate of health opportunity cost of £20,000/QALY.

This quantitative analysis comprises three components assessing INHEs of the HVCSs at the patient level, INHEs of the HVCSs at the population level, and how INHEs within the HVCSs might appropriately be rescaled to reflect expected usage across the English NHS.

The patient-level component characterises the cost, mortality and morbidity consequences of introducing CAZ-AVI over a patient's lifetime. Separate but related models were developed for the ES and MDS. In the ES, treatment with CAZ-AVI was compared to non-colistin/aminoglycoside-based treatment and colistin/aminoglycoside-based treatment (considered more toxic). In the MDS, outcomes in the overall microbiology-directed cohort using CAZ-AVI were compared to outcomes using existing AMs only.

In the ES, outcomes were modelled both for patients in whom OXA-48 Enterobacterales suspicion was confirmed and for those in whom this suspicion turned out to be incorrect. The probability of having the suspected pathogen/resistance mechanism was informed by national surveillance data supplied by PHE. The key driver of effectiveness was in vitro susceptibility (see evidence syntheses above). A combination of evidence from the literature and structured expert elicitation informed the model. Higher rates of AKI for colistin and aminoglycoside-based therapy (compared to other agents, including CAZ-AVI) were informed by 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 resulting from AKI.

The population-level component used 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 within each HVCS. This component also reflects how resistance is likely to develop to CAZ-AVI and existing AMs over time. Predictions were presented for patients initiated on treatment over the next 20 years. National surveillance data were used to estimate current numbers of patients within the HVCS and to forecast growth in patient numbers over time. A series of scenarios reflect the potential emergence of resistance to CAZ-AVI. Changes in resistance to existing AMs over time were not modelled due to the sparsity of evidence available to inform these forecasts.

Predicted overall population INHEs corresponding to the expected use of CAZ-AVI in the English NHS were generated by rescaling the population INHEs from the HVCSs to reflect additional areas of expected usage (known or suspected OXA-48 Enterobacterales bloodstream and intra-abdominal infections). Rescaling was based on surveillance data on population size and expert assessments of the similarity in per-patient INHEs between the HVCSs and these additional sites 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 summarised the extent to which these elements of value were captured within the quantitative estimates and, where this has not been possible, whether they were likely to substantively modify the quantitative estimates of value presented.

Results

Patient-level INHEs in the HVCS

The benefits of CAZ-AVI are driven by similar susceptibility but improved safety compared to colistin/aminoglycoside-based treatments, and, in the ES, by higher susceptibility than non-colistin/aminoglycoside-based treatment. The two most significant sources of uncertainty relate to the ES and are (1) the susceptibility evidence and (2) the proportion of patients in the ES who are suspected of having OXA-48 Enterobacterales who are later confirmed to have this resistant pathogen. CAZ-AVI generated INHEs of 0.16 QALYs per patient in the ES (range across scenarios 0.00–0.26) and 0.08 (0.05–0.12) in the microbiology-directed settings.

Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions were unable to select a base case for the population-level results. Population-level results are, therefore, presented for two different approaches to estimating current infection numbers (based on different methods to classify infections from clinical specimen sites), two alternative approaches to forecasting infections over time (based on whether observed trends are assumed to persist indefinitely or not) and three different trajectories with respect to CAZ-AVI resistance emergence (1%, 5% and 10% at 20 years). Across these scenarios, population INHEs varied from 531 to 2342 QALYs. The population size estimates are subject to additional uncertainties relating to the challenges of inferring patient population size from microbiology data and in forecasting population size in the future.

Estimates were generated using a number of strong assumptions about the generalisability of patient-level INHEs between settings, for example, that patient-level INHEs for bloodstream infections can be generalised to HAP/VAP infections. These assumptions were based on discussions with clinical experts.

Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions considers that it is possible that CAZ-AVI use will facilitate additional or at least more prompt receipt of required treatments/procedures for certain groups and therefore provide additional enablement value not captured within the model estimates of INHEs. The magnitude of these enablement benefits remains highly uncertain.

Conclusion

Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions's quantitative assessment of value of CAZ-AVI was associated with a base-case population INHE across its areas of expected usage of 531–2342 QALYs over 20 years. These values were informed by interlinked decision-analytic models informed by 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.

The quantitative estimates of the value for CAZ-AVI within the areas of expected usage within the NHS indicate that the maximum amount the NHS could pay for CAZ-AVI was £11 million to £47 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 CAZ-AVI. 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 CAZ-AVI?' Further methodological and quantitative work is required to address this question.

Study registration

No registration of this study was undertaken.

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