**National Institute for Health and Care Excellence**

**Antimicrobial Health Technology Evaluation**

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

Response to consultee and commentator comments on the draft scope

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Section: Background information

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Pfizer Ltd | No comment  | Noted. No action required. |
| British Thoracic Society | Yes | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | * Microorganisms don’t “adapt and become immune” to antimicrobials – rather, bacteria with mutations that prevent the activity of antimicrobials are selected for through evolutionary pressure.
* Resistance can spread through transfer of resistance genes between bacteria and also by the transfer of resistant bacteria. Transfer of resistance genes is very important when considering carbapenemase resistance.
* Infection prevention interventions including identification of patients carrying resistant bacteria, isolation, hand hygiene, environmental cleaning, are as important as antimicrobial stewardship in controlling the emergence of resistance.
* Carbapenem resistance needs further specification. The two major causes are the combination of low-level resistance mechanisms (reduced permeability, ESBL, AmpC, and drug efflux) and carbapenemase production. Within the latter, the two main types of carbapenemase enzymes are those with zinc at the active site (metallo-carbapenemases including NDM, VIM and IMP) and those with serine at the active site (KPC and OXA-48). These distinctions are important because: 1. there are a number of alternative treatment options for non-carbapenemase carbapenem-resistant bacteria, 2. Ceftazidime-avibactam is only active against serine carbapenemases.
* Gram negative bacteria (Enterobacterales such as *E coli* and *Klebsiella pneumoniae*, and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) cause a wide range of infections. Urinary tract sources account for the majority of *E coli* infections, including bloodstream infections. Other frequent infection sites include intra-abdominal and hepato-biliary infection. Other than in intensive care, these bacteria are an unusual cause of pneumonia.
* “Start smart, then focus” applies specifically to the management of patients with “red-flag” sepsis. In all other cases, empirical antibiotic treatment should aim to be as narrow spectrum as possible, based on the most frequent causative organisms and the usual antibiotic susceptibilities.
* The large majority of infections in secondary/tertiary are treated throughout the infection by empirically-chosen antibiotics without reference to positive cultures. This is because either relevant microbiological specimens are not collected prior to antibiotic initiation, cultures do not identify the bacterial cause in time to make a difference, or there is clinical indifference to the result.
 | Thank you for your comments. The background section is only intended to provide a brief description of the infections, pathogens and current management options. No action required. |
| NHS England & NHS Improvement | The background section describes what AMR is, the WHO priority pathogens and the principles of antimicrobial stewardship but doesn’t describe the background to this initiative: i.e. the reasons why a new payment model is required.  | Thank you for your comment. Please see response to comment on background by British Society for Antimicrobial Chemotherapy. No action required. |
| NHS England & NHS Improvement | Minor factual inaccuracy in the final paragraph of this section: prescribing decision 3 in Start Smart, Then Focus is to change antimicrobial (not necessarily IV). | Thank you for your comment. The background section has been updated accordingly. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | We think a useful addition would be a statement about the use of empirical versus directed therapy as for resistant infections due to the specified organisms treatment will usually be directed based on laboratory results. | Thank you for your comment. Please see response to comment on background by British Society for Antimicrobial Chemotherapy. No action required. |
| Public Health Wales  | No comments  | Noted. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: The technology / intervention

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Pfizer Ltd | Required updated to be made on marketing authorisation based on upcoming SPC correction update regarding wording of the bacteraemia licence. We would request the following wording: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.Be changed to:Ceftazidime with avibactam (Zavicefta, Pfizer Limited) has a marketing authorisation for treating in adults and paediatric patients aged 3 months and older for the following infections:* complicated intra-abdominal infections
* complicated urinary tract infections, including pyelonephritis
* hospital‑acquired pneumonia, including ventilator‑associated pneumonia
* treatment of infections caused by aerobic gram‑negative organisms with limited treatment options

Adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. | Thank you for your comment. The technology section has been updated accordingly.  |
| British Thoracic Society | Yes | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comment | Noted. No action required. |
| NHS England & NHS Improvement | No comment | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | It would be helpful given the discussion at the scoping workshop about participants’ experience of unlicensed use to note any evidence/studies in other infections e.g. CF, bronchiectasis, complicated SSTI. | Thank you for your comment. All relevant evidence will be considered by the evaluation committee. No action required. |
| Public Health Wales | No comments  | Noted. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: Population

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Pfizer Ltd | Updated required to be made to the wording of the marketing authorisation regarding the bacteraemia licence. We would request the following wording: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.

Be changed to:Adults or children aged three months or older 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 with limited treatment options

Bacteraemia in adult patients that occurs in association with, or is suspected to be associated with, any of the infections listed above.Ceftazidime with Avibactam (CAZ-AVI) may be employed in situations where there are limited treatment options hence there is real world use outside of the 3 core infection sites. Such situations are diverse but clinically important in order to realise the full potential value of anti-infectives such as CAZ-AVI, Consideration should also be given to special high-risk groups for the population modelling. For example, patients with immunosuppression, cancer chemotherapy and transplant patients are at a particular risk of infection. Such patients often have different outcomes compared with those that have a *de novo* infection and lower risk associated disease state. Application of bespoke modelling for this higher risk group is likely to give a more appropriate and comprehensive analysis of CAZ-AVI value. | Thank you for your comment. The population in the scope has been updated accordingly. |
| British Thoracic Society | * 1)In CF patients the phrase “infections caused by aerobic gram‑negative organisms with limited treatment options.” Would cover this group
* 2)CF patients may have an exacerbation of bronchiectasis with gram negative organisms , without evidence of pneumonia - so this is why point 1 above is important for this group
 | Comments noted. No action required. |
| British Society for Antimicrobial Chemotherapy | It should be recognised that the marketing authorisation is based on infections that were chosen partly because they presented the easiest way of collecting sufficient numbers of subjects for trials. In clinical practice, infections caused by carbapenem-resistant bacteria will include a range of conditions that will never be studied as part of a randomised controlled trial. Nevertheless, infection specialists will want to use ceftazidime-avibactam for these conditions. | Comments noted. No action required. |
| NHS England & NHS Improvement | Suggest extrapolate on fourth bullet point (infections caused by aerobic Gram-negative bacteria in adults with limited treatment options) to explain that treatment options may be limited for reasons of antimicrobial resistance, contra-indications or risk of drug toxicity. | Thank you for your comment. ‘Limited treatment options’ would encompass the reasons for why they are limited and aligns with the wording in the marketing authorisation therapeutic indications. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Suggest adults and children considered separately as this would be common approach in HTA. | Thank you for your comment. Ceftazidime with avibactam will be evaluated within its marketing authorisation. No action required. |
| Public Health Wales  | The indications listed in the MA are all encompassing, in that the drug can be used for complicated intra-abdominal infection, UTI, HAP / VAP and bacteraemias associated with any of the above but can also be used to treat ANY infection caused by an anaerobic Gram –ve organism with limited treatment options. This covers a wide range of indications, and in reality, this drug is likely to be used to treat a highly resistant Gram –ve organism, regardless of the site of infection. So, we are very likely going to use this drug within its’ license in the vast majority of cases. To that end, the most important indication is the last one: infections caused by Gram –ve organisms with limited treatment options (due to resistance). This will most likely be directed therapy, based on known culture and sensitivity information, and ideally the resistance mechanism.  | Thank you for your comment which is helpful for the identification of the high value clinical scenario(s). No action required. |
| MSD | MSD suggests that the term “limited treatment options” should not only focus on resistance but also pharmacokinetic/pharmacodynamic (PK/PD) considerations such as lung penetration, as PK/PD is an issue of increasing prominence from a regulatory and antibiotic choice perspective. Limited treatment options should also consider contraindications and key adverse events, including issues such as acute kidney injury. | Comment noted. ‘Limited treatment options’ would encompass the reasons for why they are limited and aligns with the wording in the marketing authorisation therapeutic indications. No action required. |
| MSD | MSD anticipates that the evaluation may primarily follow a pathogen-based approach and therefore suggest that the final scopes should be comparable across both pilot antimicrobials to allow for better comparison and avoid definition solely by the indications in the respective product labels. | Comment noted. NICE can only evaluate a technology within its marketing authorisation. The teams involved in developing the scopes have worked closely together to ensure consistency, where possible. The high value clinical scenario(s) may differ for each product.  |

## Section: Comparators

| Consultee/ Commentator | Comments [sic] | Action |
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| Pfizer Ltd | Pfizer suggests that this section is divided into two separate sections:* Empirical comparators - where there is a vast amount of options and therefore not all likely to be suitable for the economic modelling
* Confirmed comparators - where there are more limited treatment options, and therefore more suitable for economic modelling

The empirical situation is informed by the presence of risk factors or other information that suggest a high risk of MDR infection. Options in these areas are limited.**Additional Empirical Comparators:**With the above amend, Pfizer suggests the below additional comparators:* Amikacin for empirical (or combo in confirmed).
* Fosfomycin
* Temocillin
 | Thank you for your comment. The scope has been amended to cover the broad range of possible comparators used in clinical practice. As the comparators are likely to differ according to the clinical scenario (for example, comparators for ‘empiric’ treatment options will differ from those with directed treatment after microbiology results are obtained), the final scope has been amended to reflect this. The consideration of comparators at the scoping workshop has been captured and will be very helpful in specifying the high value clinical scenario(s) for detailed study. |
| British Thoracic Society | Yes – in CF combination therapy of the comparators listed are used- not just meropenem and Tobramycin , but other combinations of drugs listed | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |
| British Society for Antimicrobial Chemotherapy | With regard to the treatment of ESBL or AmpC-producing Gram negative bacteria, temocillin is a relevant comparator that should be included in the list | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |
| British Society for Antimicrobial Chemotherapy | The term “best alternative care” is a tenuous description because the evidence base to support their use is generally limited to case-series, so claiming superiority or best care is untested. This is illustrated by the diversity of treatment regimens that were included in the best alternative care arm of pivotal trials. | Comment noted. No action required. |
| NHS England & NHS Improvement | Add: amikacin; fosfomycin alone or in combination. | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Although NHS Scotland is not part of this pilot, we can advise that in Scottish practice piperacillin with tazobactam and meropenem would be main comparators. | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |
| Public Health Wales | The most common comparators are the carbapenems, of which by far the most common in the UK is meropenem. Where the organism is known or suspected resistant to carbapenems, then the only comparative treatment options are tigecycline, amikacin or colomycin IV, or possibly high dose carbapemens with the dose informed by PK/PD modelling. The other obvious comparators are the other new antibiotic / inhibitor combination drugs developed to treat these carbapenem resistant organisms, such as ceftolozane with tazobactam, or cefiderocol. | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |
| MSD | MSD considers the list of comparators to be comprehensive, except for two omissions: temocillin (covers Klebsiella pneumoniae carbapenemases (KPCs) in urinary tract infections (UTIs) and, as a narrow-spectrum penicillin, may be considered to carry particular value in antimicrobial stewardship, or AMS) and amikacin. | Thank you for your comment. Please see response to comment on comparators by Pfizer Ltd. |

## Section: Outcomes

| Consultee/ Commentator | Comments [sic] | Action |
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| Pfizer Ltd | Yes, we agree with the proposed outcomes, however, have the following amends:**Additional wording:**Pfizer would add that there should be specific reference to relevant outcomes being captured at both a population and individual level where appropriate This includes factors such as population resistance to modelled antibiotics, total country resistance, population level- mortality, number of hospital days for example. This list is not exhaustive.  | Thank you for your comment. No action required. |
| Pfizer Ltd | **Additional Outcomes**:We propose the suggested inclusion of additional outcomes to capture specific stewardship activities such as:* Number of antibiotics used in treatment cycle
* Number of appropriate treatment options given infection(s)
* Number of days of therapy

In addition, resistance / epidemiology market outcomes should be considered for inclusion:* Resistance markers: markers of population resistance / Number and severity of hospital outbreaks
 | Thank you for your comment. The outcome emergence of resistance is listed in the scope. No action required. |
| Pfizer Ltd | **Change to existing outcomes**:**“90-day mortality”** Be changed to:**“Annualised, 14-day and 28-day mortality”** Annualised mortality allows uniform modelling and comparison of interventions. However, it is important to consider shorter measures of mortality including, day and 28-day mortality at least in communicating to the wider stakeholder community. Shorter periods of mortality are more aligned to outcome measures used in the clinical trials and are more relevant clinically. It is important to note that mortality to the infection decreases significantly as time progresses. 28-day / 14-days is more relevant to microbiological eradication/test of cure and mortality outcomes. Pfizer does recognise that longer term mortality should be considered as part of the expected extended time horizon of the modelling | Thank you for your comment. The outcomes section of the scope has been updated to include days of therapy. |
| British Thoracic Society | In CF - outcomes such as reduction in exacerbation rate may also be used | Thank you for your comment. No action required. |
| British Society for Antimicrobial Chemotherapy | Infections caused by multi-drug resistant bacteria are often acquired in hospital. Patients with hospital-acquired infections are often more frail, have a greater number of co-morbidities and consequently a worse outlook compared with the average patient even before they acquire a healthcare infection. Consequently, modelling assumptions should try to identify these poorer prospects when addressing the likely value of these antibiotics to the NHS | Thank you for your comment. No action required. |
| NHS England & NHS Improvement | Outcomes should include length of antibiotic treatment course.Microbiologic eradication is a relevant outcome in terms of risk of transmission and implications for infection prevention and control (e.g. releasing side room occupancy and discharge to community settings). If any data on eradication of colonisation exist, these would be relevant to transmission. | Thank you for your comment. The outcomes section of the scope has been updated accordingly. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish  | As discussed in the meeting Adverse events should be divided into drug reactions, patient toxicity and C. Difficile. | Thank you for your comment. The outcomes section of the scope has been updated accordingly. |
| Medicines Consortium |  |  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Potential additional outcomes could be treatment failure (requiring change of treatment) and emergence of resistance to CAZ-AVI. | Thank you for your comment. The outcome emergence of resistance is listed in the scope. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Environmental cost of the antibiotic (pollution of the environment during the manufacturing of the antibiotic and residue of the antibiotic and its metabolites following excretion) - part of National Action Plan. Delivery Programme 4 – Minimise spread of AMR through the environment | Thank you for your comment. Environmental costs are not within the remit of the assessment. No action required. |
| Public Health Wales  | As well as the obvious outcome measures such as all-cause mortality (at 30 days as well as 90), clinical cure (which also needs to be defined – such as resolution of symptoms and no reoccurrence within 30 days?) and microbiological eradication, there also needs to be a recognition of the adverse effects and unintended consequences. This includes the development of resistance to this drug, driving cross resistance in other drug/bug combinations, increased prevalence of HCAIs, selecting out other resistant organisms, drug toxicity and both dose-related and idiosyncratic adverse drug reactions, drug interactions and physiological interactions. | Thank you for your comment. The outcome adverse events is listed in the scope. No action required. |
| MSD | The proposed outcome of 90-day readmission rates could perhaps be divided into two categories, namely, 90-day ITU readmission and 90-day hospital readmission. | Comment noted. The list of outcomes in the scope is inclusive**;** readmission **r**ate includes all types of readmission.  |
| MSD | MSD would also suggest that the outcome “emergence of resistance” be extended to include superinfections (e.g. increased incidence of C. difficile infection, methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant enterococci (VRE) as antibiotic use can have wider consequences). | Comment noted. The adverse events in the outcomes section of the scope has been updated accordingly. |

## Section: Economic analysis

| Consultee/ Commentator | Comments [sic] | Action |
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| Pfizer Ltd | **Additional Value Elements:**Pfizer would like to see the inclusion of productivity value as one of the additional value elements given the wider population benefit antibiotics bring to society and thus the impact on productivity at a population level.  | Thank you for your comment. The NICE methods guide does not require the inclusion of productivity value. As productivity value is not unique to antimicrobials it cannot be considered in the evaluation. No action required. |
| Pfizer Ltd | **Threshold:**We would recommend the following wording: **“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.”** Be changed to:**“flexibility will be applied to the QALY range threshold of £20,000-£30,000 as the base case, to ensure that the new approaches to valuation that may evolve in the future are appropriate to meet the overarching aims of the project and stimulate future research and development.”** This is to ensure that the overall aims of the project are not restricted by an imposed WTP threshold. In addition, the update to the NMR which reviews modifiers; severity of illness, innovation/ unmet need and uncertainty, should also be considered. Wording highlighted under the background section (page1) clearly emphasises the importance of severity of illness with wording such as;  **“These pathogens are multidrug-resistant Gram-negative bacteria that can cause severe infections in secondary care settings”** and **“For severe and life-threatening infections,”,** along with also highlighting the need for innovation **“new antimicrobials are urgently needed”** – Suggesting that there could be an overlap with workings being undertaken as part of the NICE methods review to ensure the existing QALY threshold does not become a significant burden on the valuing of medicines and limiting access for patients.  | Thank you for your comment. Sensitivity analyses will be performed for different thresholds (£15,000 and £30,000 per quality-adjusted life year) but the base-case analysis will be at £20,000 per quality-adjusted life year. No action required. |
| Pfizer Ltd | **Primary Indication:**Pfizer’s view is that the criteria outlined to identify the primary indication should also include that of Real-World Evidence where plausible. In addition, the criteria used to identify the primary indication should be dependent on the antibiotic and the proposed positioning or value it offers to society. Therefore, all criteria should be used as part of the assessment with consideration taken as to which is the most relevant for the antibiotic in question.With that unmet need could be seen to demonstrate a key area of value for CAZ-AVI. In addition, we would suggest that pathogen directed modelling is likely to generate the greatest value modelling and be more reflective of real-world practice. Further to the above, with reference to “primary Indication” being modelled; Pfizer would like to see all licenced indications modelled within the main economic model, with the ambition to cover all key indications (cUTI, cIAI, HAP/VAP, LTO, Paediatrics and Bacteraemia) and pathogen combinations to ensure a more accurate approach can be taken when extrapolating value at a population net health benefit level. An approach to modelling which considers multiple indications and pathogen combinations including several considerations to EEPRU’s value framework has been demonstrated through a dynamic disease transmission model in a recent publication1, thereby demonstrating plausibility. Sequentially, a more pragmatic approach to other indications can be taken where there is less available data, whereby Pfizer would like to see a large emphasis on the mitigation of uncertainty through expert elicitation and a practical yet novel approach to the revising of value based on gaps in data for modelling.References:1.Gordon J, Darlington O, McEwan P, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38(8):857-869. doi:10.1007/s40273-020-00906-6 | Thank you for your comments and reference. All relevant evidence will be considered by the evaluation committee. No action required. |
| British Thoracic Society | No comments | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | The selling point of this antibiotic is its activity against serine carbapenemases. Very few alternative treatments exist that have this activity. Consequently, treatment of infections caused by bacteria producing serine carbapenemases should be the primary indication used in the economic analysis. Activity of ceftazidime-avibactam against ESBL or AmpC-producing bacteria is not novel; there are a number of other beta-lactam and non-beta-lactam antibiotics that work equally well against these bacteria | Thank you for your comments. No action required. |
| NHS England & NHS Improvement | A number of different scenarios should be modelled:1. Empirical (educated guess) treatment for patients with severe or life-threatening infection judged at high risk of infection with carbapenemase-producing aerobic Gram-negative bacteria, followed by:a. Continuation of CAZ-AVI if resistant pathogen confirmedb. Stop CAZ-AVI if alternative antimicrobial option available.2. Pathogen-directed (culture and susceptibility information available) treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options.3. Pathogen-directed (culture and susceptibility information available) treatment of infections caused by aerobic Gram-negative bacteria in adults with acceptable alternative treatment options but desire to introduce diversity in choice of antimicrobials deployed. | Thank you for your comments. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Site of infection and infecting organism as informed by clinical experts and scoping consultationEnvironmental cost of the antibiotic manufacture and excretion (see above) | Thank you for your comments. No action required. |
| Public Health Wales | No comments  | Noted. No action required. |
| MSD | The inclusion of one or more primary indications in this evaluation could compromise the ability of the economic analysis to fully focus on what is of greatest value to the NHS in terms of overall unmet need and morbidity/mortality. For example, bacteraemia or a key indication such as hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP, with or without bacteraemia), would provide a more robust measure of value to the NHS than relatively “high-volume” infections such as UTI or a very common pathogen such as E. coli. | Comment noted. The ‘primary indication(s)’ will be identified based on the clinical scenario(s) that are of highest value to the NHS. ‘Primary indication(s)’ have been renamed as ‘high value clinical scenario(s)’ in the final scope. All relevant criteria will be used to identify the high value clinical scenario(s); they will not be defined solely by the most common infections/pathogens. The evaluation committee will consider evidence for both the high value clinical scenario(s) and additional indications; estimates of value to the NHS will take account of the full marketing authorisation. No further action required.  |

## Section: Equality and Diversity

| Consultee/ Commentator | Comments [sic] | Action |
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| Pfizer Ltd | No comments  | Noted. No action required. |
| British Thoracic Society | No comments | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comments | Noted. No action required. |
| NHS England & NHS Improvement | No comments | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | No issues identified. | Comment noted. No action required. |
| Public Health Wales | No comments  | Noted. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: Other considerations

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Pfizer Ltd | No comments  | Noted. No action required. |
| British Thoracic Society | No comments | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comments | Noted. No action required. |
| NHS England & NHS Improvement | Penetration to the site of infection can be ignored for the purposes of this evaluation. Beta-lactams typically penetrate equally well or equally poorly to body sites such as the lung or the bladder or the abdomen. For difficult sites such as the brain or the eye, the medical microbiologist will consider penetration within the context of measured minimum inhibitory concentration and available data on penetration before proceeding to use CAZ-AVI. | Thank you for your comment. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Helpful to include some of the discussion points from the workshop around stewardship. CAZ-AVI within local guideline? Or within Restricted/Alert/Protected policy? Or Pre-authorisation by ID/Micro required for use? | Thank you for your comment. No action required. |
| Public Health Wales | The main indication has previously been described as treating Gram –ve organisms, usually identified in blood culture, where the organism and sensitivities / resistance mechanisms are already known, with a primary site of infection at any body site. As such, a detailed understanding of PK/PD and penetration to all bodily sites is needed to understand how effective this drug will be in treating different primary infections. The other consideration is where this drug could be used *empirically* in patients at high risk / suspicion of a highly resistant infection, based upon a risk assessment for highly resistant infection or organism carriage, therefore there are a number of questions:* how many HBs / trusts screen for carriage of carbapenem resistant organisms?
* If a patient is identified as a carrier of CRO, what is the increased risk in that patient of acquiring an infection caused by that organisms, if they are a medical or surgical patient, and at what point do you empirically treat an infection with cover for that CRO?
* Has anyone developed a risk assessment for CROs separate from screening?
* If this drug is used empirically in either of the two patient groups above, what impact will this have in the volume of use, costs, drive for resistance etc.?

In the empirical treatment of suspected multi-drug resistant infection caused by CROs, what is the balance of risk associated with developing resistance and spreading these resistant organisms in the population vs mortality and morbidity in the population if you do not use this empirical model of treatment? I think this is the key question regarding empirical vs directed therapy. | Thank you for your comment. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: Questions for consultation

| Consultee/ Commentator | Comments [sic] | Action |
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| Pfizer Ltd | Pfizer responses to consultation questions:**Question 1)**Yes, except for the above change to the SPC wording the population is reflected accurately.A) Limited treatment option indication, as referred by emea1, refers to antibacterial agents or combinations expected to be clinically active against multidrug-resistant organisms (resistant to one or more classes of antimicrobial agents) for which there are limited licensed treatment options.Limited treatment options may arise due to resistance to existing treatment options or tolerability/toxicity problems determined by patient and microbiological factors: 1. Resistance (microbiological factors). For example, CAZ-AVI represents an option for treating confirmed OXA-48 resistant infection where options are exceedingly limited.

 1. Tolerability (patient factors). This may arise for example due to renal impairment; management options become limited in spite of putative antibacterial activity. In this example, the use of potential nephrotoxic agents (e.g. colistin and aminoglycosides) should be avoided leading to a limitation of available treatment options

The comprehensive licenced indications of CAZ-AVI and usage in situations where there are limited treatment options may result in use outside of the 3 core infection sites and this will be reflected in the real-world use. Given the potential for reduced barriers to use of CAZ-AVI considering this project it would be prudent to take account of this factor.Another consideration for population modelling is that there may be special high-risk groups that will be eligible for treatment. Application of bespoke modelling for this higher risk group may give a fuller and more appropriate analysis of CAZ-AVI use. For example, patients with immunosuppression, cancer chemotherapy and transplant patients will have very different associated outcomes compared to those that have a de novo infection with lower risk associations/disease states. Given the potential uses of CAZ-AVI we feel it is important to maintain holistic analysis by aggregating the value for each relevant pathogen/infection syndrome combination.References:1.European Medicines Agency (EMA); Guideline Evaluation of medicinal products indicated for treatment of bacterial infections. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3\_en.pdf , (07 Jan 2021, date last accessed). | Thank you for your comments and references. No action required. |
| Pfizer Ltd | **Question 2)****Confirmed resistant pathogen infection:** Antibiotic management of confirmed resistance would be guided by the microbiological sensitivity results obtained from such. The mechanism of resistance will be a key determinant of which agent can be used. The following table illustrating activity of the novel antimicrobials is useful aid in deciding on management options:A table showing spectrum of activity of recently marketed antibiotics AmpC, ampicillin C β-lactamase enzyme; EMA, European Medicines Agency; ESBL, extended spectrum β-lactamase; IMP, active-on-imipenem; KPC, *K. pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48; VIM, Verona integron-encoded metallo-β-lactamase. There is no comprehensive guidance on this subject. The closest example of current UK guidance for CPE/CRE is that published by the UKCPA4 in 2020. This guidance does not cover Acinetobacter or difficult to treat pseudomonas.**Suspected resistant pathogen infection:** Choice of antibacterial(s) at this stage must be considered based on microbiological factors relating to the patient (e.g. previously isolated resistant organism) or the environment (local epidemiology of bacterial resistance mechanisms). There is no guidance that exists to support this decision and treatment will be decided by the attending microbiologist. The choice of management again may be aided through knowledge of the relevant activity of the antibacterial.References:1.Electronic Medicines Compendium. Zavicefta 2 g/0.5g powder for concentrate for solution for infusion. Accessed 11/2020, 2020. <https://www.medicines.org.uk/emc/medicine/33061>2.Tamma PD, Hsu AJ. Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms. *Journal of the Pediatric Infectious Diseases Society*. 2019;8(3):251-260. Journal of the Pediatric Infectious Diseases Society 3.Electronic Medicines Compendium. Vaborem 1 g/1 g powder for concentrate for solution for infusion. Accessed 11/2020, 2020. [www.medicines.org.uk/emc/product/10813](http://www.medicines.org.uk/emc/product/10813%20) 4.<https://academic-oup-com.eu1.proxy.openathens.net/jacamr/article/2/3/dlaa075/5917871>  | Thank you for your comments and references. No action required. |
| Pfizer Ltd | **Question 3)**The chief determinant for effective treatment in resistant infection treatment is mechanism of resistance and antibacterial sensitivity. UKCPA1 and IDSA2 guidance are the two most relevant documents on this subject are chiefly pathogen oriented. Therefore, we consider pathogen directed management the most paramount need e.g. use of CAZ-AVI in OXA-48 infection. Although pathogen type/resistance mechanism is the main determinant for treatment selection there are also examples where infection site influences treatment selection: e.g.- Aminoglycosides and colistin are less appropriate agents for ventilator associated pneumonia3 - Tigecycline is only licenced for management of cIAI and cSSTI4References:1.https://academic-oup-com.eu1.proxy.openathens.net/jacamr/article/2/3/dlaa075/5917871 2.IDSA 3. www.medscape.com/answers/234753-38467/what-is-the-role-of-aminoglycosides-in-the-treatment-of-ventilator-associated-pneumonia-vap , 4. <https://www.medicines.org.uk/emc/medicine/17779/> | Thank you for your comments and references. No action required. |
| Pfizer Ltd | **Question 4)**Pfizer’s view is that the criteria outlined to identify the primary indication should also include Real-World Evidence where plausible. In addition, the criteria used to identify the primary indication should be dependent on the antibiotic and the proposed positioning or value it offers to society. Therefore, all criteria should be used as part of the assessment with consideration taken as to which is the most relevant for the antibiotic in question.With that unmet need could be seen to demonstrate a key area of value for ceftazidime / avibactam (CAZ-AVI). In addition, we would suggest that pathogen directed modelling is likely to generate the greatest value modelling. Approaches to modelling multiple indications and pathogen combinations which includes several considerations to EEPRU’s value framework has been demonstrated through a dynamic disease transmission model in a recent publication1, thereby demonstrating its plausibility. Sequentially, a more pragmatic approach to other indications can be taken where there is less available data, whereby Pfizer would like to see a large emphasis on the mitigation of uncertainty through expert elicitation and a practical yet novel approach to the revising of value based on gaps in data for modelling.References:1.Gordon J, Darlington O, McEwan P, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38(8):857-869. doi:10.1007/s40273-020-00906-6 | Thank you for your comments and reference. No action required. |
| Pfizer Ltd | **Question 5)**Resistance mechanism (pathogen) directed modelling is likely to generate the most appropriate value modelling for CAZ-AVI. In cases that require management of resistance Gram negative infection, the options are limited and may include those illustrated in table 1. If resistance mechanism activity is considered as the proxy for intervention a wider realm of evidence will be available. Data/studies for CRE active interventions (other than CAZ-AVI) as a whole could be considered in a meta-analysis approach to contribute to the body of evidence and allow more robust modelling. In other words, isolating antibiotic specific literature for analysis in this area could limit the potential of value modelling. Consideration should be given to modelling 1. Early targeted therapy (“empirical” situations associated with risk factors) – the benefits at this stage on cure and survival are likely to be the greatest

Colistin, temocillin, fosfomycin and aminoglycosides are among the other potential options here, but this is not exhaustive or illustrated any clear guidance since these decisions are usually made.Given the potential uses of CAZ-AVI we feel it is important to maintain holistic analysis by aggregating the value for each relevant pathogen/infection syndrome combination. HAP/VAP caused by MDR organisms may be associated with high value modelling for CAZ-AVI, this area is associated with a high prevalence and severe outcomes and is therefore perceived to have a very high unmet need and value for intervention with CAZ-AVI. In lieu of a UK HAP/VAP guideline, there is a European consensus guideline1 which recommends antibiogram/pathogen-based guidance. Empirical treatments for non-resistant HAP in the UK include co-amoxiclav, doxycyline, clarithromycin and levofloxacin. Treatment of VAP is usually determined locally according to antibiogram based management.References:1. *European Respiratory Journal*. 2017;50(3):1700582 | Thank you for your comments and reference. No action required. |
| Pfizer Ltd | **Question 6)**In considering pathogen diagnostics for Gram-negative aerobic infection it is necessary to consider broadly the types of infection relevant to CAZ-AVI; namely, P. aeruginosa, ESBL and carbapenem resistant Enterobacterales (CRE/CPE). Technologies employed will differ according to the trust and the suspected pathogen and suspected site of infection.***Pathogen diagnosis for incident infection***Patients that present a fever or have fever during a hospital inpatient stay should have blood and suspected infection site sampling to detect appropriate organisms. The process of full culture and sensitivity may take 48-72 hours in such cases and includes the use of automated and manual AST methods. The particular technology employed locally is trust dependent.A full sensitivity analysis or molecular diagnostic may be required, and smaller trusts will need to send the sample to the PHE Bacteriology reference department (BRD) to complete this. This can be associated with quite a significant delay to full identification of the pathogen(s) and their resistance mechanism.***Pathogen diagnosis for suspected CPE/CRE infection***PHE have outlined a framework for detection and containment of CPE. A newly awaited resource for is underway which underwent consultation in 2020.1: At the essence of this guidance is CRE/CPE risk factor scoring for all emergency and elective patient admissions who may or may not present with signs of infection. The guidance recognises that there is evidence to support CPE colonisation precedes invasive infection, therefore when risk factors are detected, targeted rectal screening for CRE/CPE is undertaken. All patients in augmented care or high-risk units should also be screened as a routine measure. The following patients should be strongly considered for screening on admission if they are likely to stay in hospital overnight:* If, in the last 12 months:
	+ been previously identified as CPE positive
	+ been an inpatient in any hospital, both in the UK or abroad
	+ had multiple hospital treatments e.g. are dialysis dependant or have had cancer chemotherapy
	+ had known epidemiological link to a known carrier of CPE (includes household and care home contacts of known cases)
* Patients admitted into augmented care or high-risk units
* Other risk factors associated with increased risk and should be considered for screening are:
	+ Patients with immunosuppression
	+ Patients with exposure to broad-spectrum antibiotic courses (such as cephalosporins, glycopeptides, and piperacillin/tazobactam) and in particular carbapenems within the past one month, not covered in other risk groups e.g. those receiving OPAT
	+ Patients admitted from Long Term Care Facilities where higher levels of interventional care are provided e.g. long-term ventilation

Furthermore Boyd et al.2 have also validated a bedside scoring criterion for patients in UK critical care environments to allow for identification and appropriate therapy as early as possible. This result can be obtained within hours and is available to all trusts. If detected and there are signs of infection it would be prudent to cover for resistant infection (e.g. with CAZ-AVI) until full results are obtained. When CPE/CRE is detected through rectal screening, molecular characterisation of the resistance mechanism is undertaken either locally if resources allow or if not are sent to the PHE BRD as above with inherent associated delay.References: 1.<https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926563/Framework_of_actions_to_contain_CPE-draft.pdf> 2.<http://www.sciencedirect.com/science/article/pii/S2213716520301855> | Thank you for your comments and references. No action required. |
| Pfizer Ltd | **Question 7)**Answered in above response under Outcomes section. | Noted. No action required. |
| Pfizer Ltd | **Question 8)**This has been outlined in the response to question 6. Again, we re-emphasise the importance of PHE risk scoring to fully define the eligible population.  | Noted. No action required. |
| Pfizer Ltd | **Question 9)**Answered in above response under Equality section. | Noted. No action required. |
| Pfizer Ltd | **Question 10)**Pfizer expect the project to deal with current barriers to adoption and the project should be modified based on learnings / outcomes. However, the variability in diagnostics across the UK will continue to present a barrier based on current practice | Thank you for your comment. No action required. |
| British Thoracic Society | No comments | Noted. No action required. |
| British Society for Antimicrobial Chemotherapy | * Limited treatment options should restrict use to infections where at a maximum only two other antibiotics are reasonable options, based on pharmacodynamic factors (antibiotic susceptibility) pharmacokinetic features (site of infection, patient administration options, metabolism or excretion considerations) or patient factors (adverse reactions).
* Piperacillin-tazobactam and meropenem are antibiotics that are frequently used for the treatment of multi-resistant bacteria. Other established choices include aminoglycosides (gentamicin, amikacin, tobramycin), colistin, tigecycline, used either singly or in combination.
* Generally, treatment options are the same for most infection sites, partly based on good PK/PD characteristics and partly because of limited alternatives.
* Primary indication should include the criterion that this antibiotic is a scare and valuable resource that will become less effective if/when resistance to the antibiotic emerges and that resistance emergence will be accelerated by increased use.
* Highest value indication for ceftazidime –avibactam is treatment of infection caused by KPC or OXA-48-producing bacteria. Important comparators are: for KPC – cefiderocol, imipenem-relebactam, meropenem-vaborbactam. For OXA-48 – cefiderocol. Other antibiotics may be effective on a case-by case basis, according to susceptibility testing results.
* Testing strategies are based on EUCAST criteria (see <https://www.eucast.org/clinical_breakpoints/> ) and 8. UK Standards for Microbiology Investigations. Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases). 30 September 2020. Available from: <https://www.gov.uk/government/publications/smi-b-60-detection-of-bacteria-with-carbapenem-hydrolysing-lactamases-carbapenemases> .
* Stewardship scenarios vary widely from hospital to hospital. However, an essential stewardship feature that should be required under the delinkage scheme is the need for prior authorisation from an infection expert before the drug can be prescribed/dispensed.
* An important barrier to adoption is the availability of rapid identification of carbapenemase. Not all labs currently have access to PCR tests for this.
 | Thank you for your comments and website references. No action required. |
| NHS England & NHS Improvement | No comments | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *Does the population reflect those that would be eligible to receive ceftazidime with avibactam in the NHS in England?*
	1. *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?*

As mentioned previously patients with other types of infection (CF, bronchiectasis, cSSTI) should be included.1. Limited treatment options could reflect patient factors such as renal impairment and prior resistant infections.
 | Thank you for your comment. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *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?*

Already answered. | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *Do established treatments differ according to infection site in people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?*

Yes, depends on the ability of an antibiotic to penetrate the infected tissues.  | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *What criteria should be used to identify the primary indication(s) for the economic analysis?*
	1. *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*](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf)*.*In addition to the greatest unmet need and benefit to public health the primary indication should be reflective of the experts views otherwise the population for the HTA evaluation will be drawn into question.Consideration should be given to the quality and quantity of evidence available to produce robust estimates of population health benefit when selecting the primary indication(s).Environmental impact (see above in Outcomes). | Thank you for your comment. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *In which indication(s) is ceftazidime with avibactam expected to have the highest value when considering the criteria listed under question 4.a?*
	1. *What are the most important comparators for this indication(s)?*

HAP/VAPa.Piperacillin with tazobactam and meropenem. | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *What testing strategies are used in clinical practice for people with severe infections due to aerobic gram-negative bacteria where resistance is suspected?*

1) Empirical diagnosis and risk assessment on the likelihood of infection with a multi-resistance pathogen based on individual’s past microbiological history, local epidemiology and whether associated with an outbreak.2) Laboratory results from clinical specimens such as blood cultures, swabs. | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *Are the outcomes listed appropriate?*

Yes | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *What stewardship scenarios are relevant to be considered in the analysis?*

Risk-based empirical useDirected use | Noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. *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.*No issues identified. | Noted. No action required. |
|  | 1. *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.*

Yes, not all automated susceptibility testing platforms include CTZ/AVI. Therefore additional testing required adding delay and cost into the system.Not all laboratories have the ability to detect the resistance genotype. | Thank you for your comment. No action required. |
| Public Health Wales  | No comments  | Noted. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: Additional comments on the draft scope

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Pfizer Ltd | No comments  | Noted. No action required. |
| British Thoracic Society | CF patient with more advanced disease, and lower lung function may require treatment for infections caused by aerobic gram negative organisms with limited treatment options. This new Antibiotic is welcomed in this context and would only apply to as small number of patients | Thank you for your comment. No action required. |
| British Society for Antimicrobial Chemotherapy | No comments | Noted. No action required. |
| NHS England & NHS Improvement | Public Health England complies routine data on the species and number of isolates of carbapenem-resistant and multi-drug-resistant bacteria reported by laboratories around the UK, which will be helpful to evaluate potential patient numbers and budget impact. Summary reported in annual ESPAUR report: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report The scope won’t include defined place in therapy for these two products and NHSE&I expects that place in therapy and conditions for use (e.g. micro approval only) will continue to be for local determination. | Thank you for your comment and reference. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | No comments | Noted. No action required. |
| Public Health Wales  | By removing cost as an issue, you open up a series of questions around how this drug is going to be used, empirically or as directed therapy, and the development of resistance becomes much more important as a negative outcome. Whilst I appreciate the financial considerations in using the ‘subscription’ model of funding for this drug, my concern is that this could actually *increase* the volume of use of this drug, so driving resistance, whereas the whole intention was to keep this drug for last-line specialist use only, so preserving its efficacy and reducing the drive on resistance. The HTA should very carefully consider empirical vs directed therapy, the behaviour of clinicians and ultimately the development of resistance. This has to be the primary outcome. | Thank you for your comment. No action required. |
| MSD | No comments | Noted. No action required. |

## Section: Provisional list of consultees and commentators

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| MSD | Sepsis Trust not included in the provisional list. | Comment noted. Sepsis Trust has been added as a consultee to the patient/carer section of the stakeholder list. |

**The Royal College of Physicians would like to endorse the responses submitted by the British Thoracic Society.**