Professional and NHS organisation submission template [Note, this is Dr Seaton’s clinical expert statement]

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

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| Thank you for agreeing to give us your organisation’s views on this technology and its possible use in the NHS.  You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.  To help you give your views, please use this questionnaire. **You do not have to answer every question** – they are prompts to guide you. The text boxes will expand as you type.  **Information on completing this submission**   * Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable * We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. * Your response should not be longer than 13 pages. |

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| **About you** |  |
| 1. Your name | Dr R. Andrew Seaton |
| 2. Name of organisation | NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital, Glasgow |
| 3. Job title or position | Consultant in Infectious Diseases and General Medicine. Infectious Diseases Physician, Antimicrobial Stewardship lead for NHS Greater Glasgow and Clyde and Chair of the Scottish Antimicrobial Prescribing Group: Antimicrobial Guidance, Formulary and Stewardship are a key area of interest and work. |
| 4. Are you (please tick all that apply): | X an employee or representative of a healthcare professional organisation that represents clinicians?  X a specialist in the treatment of people with this condition?  a specialist in the clinical evidence base for this condition or technology (for example, an investigator in clinical trials for the technology)?  commissioning services for a CCG or NHS England in general?  commissioning services for the condition for which NICE is considering this technology?  responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?  other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | British Society Antimicrobial Chemotherapy – charitable status I am also chair of the Scottish Antimicrobial Prescribing Group which is funded by the Scottish Government |
| 5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the stakeholder list.]  If so, please state the name of manufacturer, amount, and purpose of funding. | No |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | No |
| **Current treatment of severe gram-negative infections, where resistance is suspected/confirmed** |  |
| 6. What is the main aim of treatment? | To cure infection in individual patients  To support the limitation of carbapenem antibiotics as part of an antimicrobial stewardship (AMS) strategy |
| 7. What do you consider a clinically significant treatment response? | Dependent on site of infection. Broadly: clinical improvement such that antibiotic therapy is discontinued with no clinical or microbiological relapse within 28-30 days |
| 8. In your view, is there an unmet need for patients and healthcare professionals? | Yes. Multidrug resistant Gram negative infections are increasingly recognised and treatment options are limited. Escalating carbapenem use is associated with development of resistance and further rlimitation of treatment options  We need alternatives to empirical carbapenem use in high risk settings. Ceftaz/Avibactam may be part of that AMS strategy |
| 9. How is the condition currently treated in the NHS? | Depending on the clinical situation and nature of the resistance mechanism treatment will vary: Colistin + Meropenem, Tigecycline + Meropenem, Colistin + Amikacin + Meropenem. Ceftaz/Avibactam in this context may be co-prescribed with anther agent such as meropenem.  In addition Ceftaz/Avibactam may be used as a carbapenem sparing agent as part of an AMS initiative. In this case it would be used as an alternative to meropenem e.g. in ESBL infections |
| * Are any clinical guidelines used in the treatment of the condition, and if so, which? | [Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party† | Journal of Antimicrobial Chemotherapy | Oxford Academic (oup.com)](https://academic.oup.com/jac/article/73/suppl_3/iii2/4915406?login=true)  Treatment is tailored to individual patients and the organism isolated. This is a useful guide from BSAC |
| * Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | Well defined in that treatment is very much led by clinical microbiologists based on the resistance profile of the organism isolated and the tolerability of the regimen (including renal and hepatic function).  Treatment choices poorly defined as very much individualised.  Laboratory diagnostics are crucial to guide tailored treatment |
| * What impact would the technology have on the current pathway of care? | It would be a welcome addition to the available antimicrobial options. It would likely be used as a carbapenem sparing antibiotic to limit carbapenem resistance. Particularly useful in antimicrobial stewardship initiatives in critical care and haemato-oncology units where such MDR Gram negative infections are more prevalent. Its use would be limited to specialist initiation under microbiology/infection specialist direction |
| **The use of the technology** |  |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | Ceftaz/Avibactam is already used variably in the UK based on locally adapted non-formulary processes and it is likely it will continue to be used in a similar way. It may be used more readily particularly in stewardship initiatives to control carbapenem prescribing in certain epidemiological situations. |
| * To what extent and in which population(s) is the technology being used in your local health economy? | Use is limited to clinical microbiology initiation in Critical care, Haemato-oncology, Cystic fibrosis and Renal units. In Scotland at least use is very low volume currently |
| * How does healthcare resource use differ between the technology and current care? | Use of Ceftaz/Avibactam is more readily used in large teaching hospitals with greater case mix and complex patient groups. Its use is restricted in that it requires clinical microbiology authorisation and non-formulary authorisation process to be completed. Only used if no alternative agents are available. Currently not used systematically for control of carbapenem use i.e. used for specific patient treatment but not within existing stewardship initiatives |
| * What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | None |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Yes – as both an alternative treatment option (to meropenem) and as an AMS tool to reduce carbapenem prescribing and resistance |
| * Do you expect the technology to increase length of life more than current care? | No. The benefit is to provide an alternative treatment for patients and to augment/facilitate organisational AMS initiatives  Caveat: Some published retrospective data suggests a possible survival advantage in some clinical situations but this has not been proved in robust clinical trials which are designed for non-inferiority |
| * Do you expect the technology to increase health-related quality of life more than current care? | Probably not although if carbapenem use is reduced as a consequence there may be significant ecological and public health benefits (e.g. reduction in Carbapenemase producing organisms in critical care) |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | Drug interactions or other patient factors (e.g. allergy, intolerability, renal failure) may sometimes limit use of alternative antibiotics |
| 13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | No – similar. No additional practical considerations |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Use will be led/initiated by infection specialists - including as part of a specific AMS initiative to spare carbapenems  Testing for sensitivity within the microbiological laboratory |
| 15. What is the outcome of any evaluations or audits of the use of the technology? | Observational and RCTs demonstrate benefits in MDR GN infections – non-inferiority to carbapenems in specific clinical and microbiological situations (e.g. ESBL infections) |
| **Sources of evidence** |  |
| 16. Do the clinical trials on the technology reflect current UK clinical practice? | No. The drug is used infrequently and the reality is it would be used for:   1. Specific patients (with MDR infection) rather than clinical conditions (intra-abdominal infection/ complex UTI) 2. Specific AMS initiatives – a means to target reduction in carbapenems |
| * If not, how could the results be extrapolated to the UK setting? |  |
| * What, in your view, are the most important outcomes, and were they measured in the trials? | Non-inferiority in intra-abdominal and complex urinary tract infections including bacteraemia. Non-inferiority implies an alternative treatment (to carbapenems) can be utilised in some situations a sdetemrined by infection specialists |
| * If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | Clinical trials examine cure vs failure of treatment usually at 28-30 days post treatment |
| * Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | Not that I am aware of although there would be concern for *C. difficile* if use of this agent were to become uncontrolled – this should be prevented by infection specialist control of the agent. |
| 17. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 18. How do data on real-world experience compare with the trial data? | There is not widespread use of this agent as yet due to its non-formulary status. Most data therefore comes from either clinical trials or compassionate use. |
| **Equality** |  |
| 19. Are there any potential [equality issues](https://www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme) that should be taken into account when considering this treatment? | Not that I am aware of |
| 20. Consider whether these issues are different from issues with current care and why. |  |
| **Key messages** |  |
| 21. In up to 5 bullet points, please summarise the key messages of your submission. | * **Antimicrobial stewardship**: Urgent need for antimicrobials to (when required) **substitute** carbapenems to minimise carbapenem resistance and preserve their future use * **Direct patient care:** Urgent need for antimicrobials to **augment the available agents** in treatment of multidrug resistant Gram negative infections * Evidence of non-inferiority to carbapenems in some key clinical situations which allows this agent to be considered for targeted use as above * Potential benefits over other agents where toxicity / treatment failure may be higher (e.g. Colistin, Tigecycline) |

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