Professional and NHS organisation submission template

Cefiderocol 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 | xxxxxxxxxxxxxxx |
| 2. Name of organisation | UK Cystic Fibrosis Medical Association |
| 3. Job title or position | xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| 4. Are you (please tick all that apply): | an employee or representative of a healthcare professional organisation that represents clinicians?  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). | **The UKCFMA supports the work of specialist medical clinicians in the UK in improving clinical outcomes for people with CF through**   * **Consultation and communication with members to develop and promote representative positions/statements** * **Providing evidence and value-based care in line with best international standards** * **Working collaboratively with partner and stakeholder organisations** * **Developing and supporting processes of quality improvement** * **Supporting Training and Career Development**   **The UKCFMA does not receive any funding. Some administrative time has been provided to the CFMA by the CF Trust.** |
| 4b. 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? | In cystic fibrosis (CF), the aim of treatment of severe gram-negative infections is to control the acute exacerbation of an infection. In most cases, people with CF will have chronic infection with gram-negative organisms (most commonly Pseudomonas aeruginosa) and it will be a flare in these bacteria (either an increase in bacterial numbers or an increase in the virulence of the bacteria) that will cause the acute exacerbation. In the majority of cases of treatment of severe gram-negative infections in CF we are not expecting bacterial eradication. |
| 7. What do you consider a clinically significant treatment response? | A clinically significant treatment response can be evaluated in a number of ways in CF exacerbations:   1. Resolution of inflammatory markers – total white cell count and C-reactive protein are used to evaluate infections and the normalisation of these values suggest a treatment response 2. Lung function – In CF, a spirometry measure, the Forced Expiratory Volume in 1 minute (FEV1) has been shown to be a good clinical marker of an exacerbation with acute declines in value seen with acute exacerbations. A decline of >10% in FEV1 is considered significant and a recovery of FEV1 to within 10% of the previous stable baseline would be considered a clinically significant treatment response. |
| 8. In your view, is there an unmet need for patients and healthcare professionals? | Yes, due to the chronic nature of gram-negative infections in CF, the bacteria mutate and develop bacterial resistance to commonly used antibiotics. Also given the frequent use of antibiotics in CF, some people develop multiple antibiotic allergies and intolerances that mean a reduced choice of antibiotic therapies to treat acute exacerbations |
| 9. How is the condition currently treated in the NHS? | In CF, severe gram negative infections are usually treated with a combination of intravenous antibiotics, mostly involving an antibiotic from the beta-lactam group (such as a cephalosporin, a carbapenem or alternatives such as aztreonam, Fosfomycin or tazobactam-piperacillin) combined with an aminoglycoside antibiotic or colistin. For very severe infections caused by multi-resistant organisms a combination of 3 or 4 antibiotics may be used. |
| * Are any clinical guidelines used in the treatment of the condition, and if so, which? | CF Trust Consensus Document – Antibiotic Treatment in CF. Third Edition 2009Pulmonary Exacerbations Clinical Care Guidelines: Executive Summary Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC, Clinical Practice Guidelines for Pulmonary Therapies Committee. [Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations](http://www.atsjournals.org/doi/full/10.1164/rccm.200812-1845PP). Am J Respir Crit Care Med. 2009 Nov 1;180(9):802-8. doi: 10.1164/rccm.200812-1845PP. Epub 2009 Sep 3. |
| * 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.) | All CF clinicians in the UK would treat a severe gram negative infection with at least two intravenous antibiotics for a period of at least 10 days. The choice of antibiotic will vary depending on patient factors (such as allergy/intolerance and bacterial sensitivity) and local hospital factors such as availability of antibiotic preparations as well as physician preference. |
| * What impact would the technology have on the current pathway of care? | The technology would allow a further antibiotic to be available when considering treatment. It wouldn’t change the pathway of care but would be an alternative in the beta-lactam group and may have particular use in carbapenem resistant organisms |
| **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? | Yes the treatment will be given in the same was as other intravenous antibiotics |
| * To what extent and in which population(s) is the technology being used in your local health economy? | I am not aware of its current use in my local health economy |
| * How does healthcare resource use differ between the technology and current care? |  |
| * What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | Nil |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | For carbapenem resistant gram negative infections we may see better response to IV therapy as measured by the time for resolution of inflammatory markers and improvement in lung function |
| * Do you expect the technology to increase length of life more than current care? | In some cases of very severe infections not responding to currently available antibiotics, the use of cefiderocol may increase life expectancy |
| * Do you expect the technology to increase health-related quality of life more than current care? | If cefiderocol can treat an acute exacerbation of a gram negative organism and then prolong time to next infection then this will improve health related QoL. Of note this study hasn’t been done as this drug has limited data for use in CF patients |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | No, anyone with an infection due to carbapenem-resistant organisms would benefit from this drug. Such people are more likely to be people with chronic gram negative infections such as CF or other forms of bronchiectasis. It may also be of more benefit to patients in an ICU setting with ventilator associated pneumonia |
| 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.) | **Cefiderocol requires a slow infusion over 3 hours. This will limit patient tolerability for people with CF who, in my experience, prefer bolus or short-infusion antibiotics so as not to spend a significant amount of the day attached to an infusion. In CF many people are treated with home intravenous antibiotics and the slow infusion time will limit that ability to do this due to the requirement for IV pumps** |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | **Sensitivity testing of the organism to cefiderocol prior to commencing treatment.** |
| 15. What is the outcome of any evaluations or audits of the use of the technology? | - |
| **Sources of evidence** |  |
| 16. Do the clinical trials on the technology reflect current UK clinical practice? | **The clinical trials of cefiderocol mostly reflect the UK clinical practice and follow the licence of the medication – complex urinary tract infections (Portsmouth et al 2018) and ventilator associated pneumonia in the critical care setting (Wunderink et al. 2021 APEKS-NP trial). The CREDIBLE-CR trial (Bassetti et al., 2021) also looked at these cohorts but had a focus on carbapenem-resistant organisms. No clinical trial has been done to look at the use of cefiderocol in CF patients.** |
| * If not, how could the results be extrapolated to the UK setting? | **It is difficult to directly extrapolate the data to use in CF patients as the outcome measures are different, the APEKS-NP trial which looked at pneumonia (and therefore the most similar to CF exacerbations) had all-cause mortality as the primary outcome measure. In CF, we would be looking at improvements in spirometry measures and time to next infection as the most valid outcome measures, alongside quantitative microbiology to see the effect of the antibiotic on bacterial numbers.** |
| * What, in your view, are the most important outcomes, and were they measured in the trials? | **In CF it would be as above – spirometry measures and time to next infection. As CF was not included in any of the studies they were not measures** |
| * If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | - |
| * Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | **Not that I am aware of** |
| 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? | **Bleibteu et al, 2021 (doi; 10.3390/microorganisms9020282) described the first cases of prescriptions and the efficacy of cefiderocol in the French compassionate programme. They demonstrated the importance of susceptibility testing with 6/7 susceptible strains responding to therapy and 0/5 non-susceptible strains responding.** |
| **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? | **No** |
| 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. | * **A new antibiotic preparation that is indicated for carbabenem-resistant organisms** * **Would be a useful addition for treating chronic gram-negative bacterial infections seen in CF infections** * **The slow infusion time may reduce its use in CF population due to patient preference** * **Susceptibility testing should be used to guide therapy** |

Thank you for your time.

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