NICE advice

Antimicrobial prescribing: Ceftazidime/avibactam

Evidence summary
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Overview

This evidence summary outlines the best available evidence for a new intravenous antimicrobial, ceftazidime/avibactam (Zavicefta). It is indicated for treating:

- complicated intra-abdominal infections
- complicated urinary tract infections, including pyelonephritis
- hospital-acquired pneumonia, including ventilator-associated pneumonia
- infections caused by aerobic gram-negative organisms in adults with limited treatment options.

See our 2-page summary to support local decision making which includes data on effectiveness, safety, patient factors, resource impact and resistance.

Regulatory status and indications

Ceftazidime/avibactam (Zavicefta, Pfizer Limited) received a marketing authorisation in June 2016 and was launched in the UK in March 2017. Ceftazidime/avibactam is a combination antimicrobial that consists of a third generation cephalosporin, ceftazidime and a non-beta-lactam, beta-lactamase inhibitor, avibactam.

Ceftazidime/avibactam is indicated for treating complicated intra-abdominal infections, complicated urinary tract infections, including pyelonephritis, hospital-acquired pneumonia, including ventilator-associated pneumonia, and infections due to aerobic gram-negative organisms in adults with limited treatment options.

For full information see the summary of product characteristic (SPC): ceftazidime/avibactam.

Adults aged 18 years and over

Antimicrobial	Dosage and course length[a] in adults with estimated creatinine clearance of 51 ml/min or more
Ceftazidime/ avibactam	2 g/0.5 g every 8 hours administered by intravenous infusion over 2 hours • Complicated intra-abdominal infections[b,c]: duration 5 to 14 days • Complicated urinary tract infections[c] including pyelonephritis: duration 5 to 10 days[d] • Hospital acquired pneumonia, including ventilator-associated pneumonia[c]: duration 7 to 14 days • Infections due to aerobic gram-negative organisms in adults with limited treatment options[b,c]: duration is guided by severity of the infection, the pathogen(s) and the person's clinical and bacteriological progress[e]

[a] Dose and course length taken from the SPC for ceftazidime/avibactam. Adults with an estimated creatinine clearance of 50 ml/min or less require the dose of ceftazidime/avibactam to be adjusted.

[b] Use in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.

[c] Use in combination with an antibacterial agent active against gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

[d] The total duration shown may include intravenous ceftazidime/avibactam followed by appropriate oral therapy.

[e] There is very limited experience with the use of ceftazidime/avibactam for more than 14 days.

Key messages

This evidence summary – antimicrobial prescribing discusses 3 published randomised controlled trials (RCTs) (REPRISE [Carmeli et al. 2016], RECLAIM 1 and 2 [Mazuski et al. 2016] and RECAPTURE 1 and 2 [Wagenlehner et al. 2016]). RECLAIM 1 and 2 included adults with complicated intra-abdominal infections and RECAPTURE 1 and 2 included adults with complicated urinary tract infections. Both studies included 2 RCTs that were reported as pooled results and the populations had ceftazidime-resistant and -susceptible pathogens. REPRISE was an open-label RCT that examined the efficacy of ceftazidime/avibactam in adults with complicated intra-abdominal infections and in adults with complicated urinary tract infections with only ceftazidime-resistant pathogens. The majority of the population (92%) in REPRISE had complicated urinary tract infection. There were no published studies to assess the efficacy and safety of ceftazidime/avibactam in adults with hospital-acquired pneumonia and gram-negative infections with limited treatment options.

Ceftazidime/avibactam was found to be non-inferior in terms of primary outcomes (see the 2-page summary) to meropenem and doripenem (not available in the UK) for the treatment of complicated intra-abdominal infections and complicated urinary tract infections respectively in adults with ceftazidime-resistant and -susceptible pathogens (RECLAIM 1 and 2 and RECAPTURE 1 and 2). Similar clinical cure rates were found between ceftazidime/avibactam and best available treatment (mainly with imipenem and meropenem) in REPRISE and there was no statistical comparison conducted between the 2 groups.

The safety profile of ceftazidime/avibactam has generally reflected that already known for ceftazidime alone. However, it is not possible to draw any definitive conclusions regarding the possible effects of avibactam on the adverse event profile of ceftazidime (European Public Assessment Report [EPAR]: ceftazidime/avibactam).

See the 2-page summary for further information on efficacy, safety and resistance.

Resource impact

The acquisition cost of ceftazidime/avibactam is higher than other intravenous antimicrobials that are commonly used for complicated intra-abdominal infections, complicated urinary tract infections and hospital acquired pneumonia. A vial of ceftazidime/avibactam 2 g/0.5 g costs £85.70 excluding VAT (British National Formulary [BNF], October 2017).

Ceftazidime/avibactam is an intravenous antimicrobial that was studied mainly in hospitalised people. In practice, ceftazidime/avibactam will be prescribed and administered within a hospital setting. Ceftazidime/avibactam is not included on the high cost drug exclusions list and so from a commissioning perspective the tariff for the inpatient episode will remain the same whichever antimicrobial is used for the indications discussed in this evidence summary.

Current guidance

- There are no UK based guidelines for the management of complicated intra-abdominal infections or complicated urinary tract infections in adults. NICE is developing an antimicrobial prescribing guideline on managing complicated urinary tract infections.
- For the treatment of hospital-acquired pneumonia see the NICE guideline on pneumonia.
- Other resources include the NICE guidelines on antimicrobial stewardship: systems and processes for effective antimicrobial use and antimicrobial stewardship: changing risk-related behaviours in the general population. Public Health England's Start smart – then focus toolkit, guidelines by the European Association of Urology Guidelines on urological infections (2015), Surgical Infection Society and the Infectious Diseases Society of America and the World Society of Emergency Surgery.

Place in therapy

Published data were available for the use of ceftazidime/avibactam for complicated intra-abdominal infections and complicated urinary tract infections in adults. There were no published randomised controlled trial (RCT) data for using ceftazidime/avibactam to treat hospital-acquired pneumonia or to treat aerobic gram-negative infections with limited treatment options and so the likely place of therapy for these 2 indications is unclear.

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of ceftazidime/avibactam for its licensed indications. The European Public Assessment Report [EPAR]: ceftazidime/avibactam states that ceftazidime/avibactam is active against ceftazidime-resistant and many carbapenem-resistant clinical isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* when assessed in vitro and in vivo. However, there is limited evidence that ceftazidime/avibactam is effective in treating people with ceftazidime-resistant pathogens. The EPAR also states that very few pathogens expressing serine carbapenemases have been treated with ceftazidime/avibactam. Specialists involved in reviewing this evidence summary have suggested that ceftazidime/avibactam is likely to be a treatment option for complicated intra-abdominal infections and complicated urinary tract infections if a

person's infection does not respond to commonly used antimicrobials and when there is known resistance to other antimicrobials. Use of ceftazidime/avibactam will need to be informed by understanding the mechanisms by which pathogens evolve to develop resistance.

Commissioners and local decision makers will need to consider where ceftazidime/avibactam fits within local hospital antimicrobial policies and guidelines for managing complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia and treating infections due to aerobic gram-negative organisms in adults with limited treatment options, taking account of the principles of antimicrobial stewardship.

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