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NICE advice

Antimicrobial prescribing: ceftolozane with tazobactam for treating hospital-acquired pneumonia, including ventilator-associated pneumonia

Evidence summary
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Key messages

The content of this evidence summary was up to date in December 2019. See summaries of product characteristics (SPCs), British National Formulary (BNF), or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Ceftolozane with tazobactam (Zerbaxa, Merck Sharp & Dohme Limited) is a combination of

a cephalosporin antibiotic, which predominantly covers Gram-negative bacteria, and a beta-lactamase inhibitor, which inhibits many (but not all) class A beta-lactamases (enzymes that cause resistance to beta-lactam antibiotics). It is given as a 1-hour intravenous (IV) infusion every 8 hours.

Ceftolozane with tazobactam received a marketing authorisation for treating complicated intra-abdominal infections, acute pyelonephritis and complicated urinary tract infections in adults in September 2015 (see the evidence summaries on complicated urinary tract infections: ceftolozane/tazobactam and complicated intra-abdominal infections: ceftolozane/tazobactam for more information). In August 2019, the indication for ceftolozane with tazobactam was extended to include treating hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults (Zerbaxa: Procedural steps taken and scientific information after authorisation).

Evidence for using ceftolozane with tazobactam for treating HAP and VAP is from 1 phase 3 randomised controlled non-inferiority trial (ASPECT-NP). ASPECT-NP found that a high dose of ceftolozane with tazobactam was non-inferior to meropenem for treating seriously ill people with VAP or ventilated HAP (see the section on effectiveness for definition) caused by Gram-negative pathogens such as Pseudomonas aeruginosa (including multidrug-resistant strains) and Enterobacterales (formerly known as Enterobacteriaceae, including producers of extended-spectrum beta-lactamases [ESBL]). Rates of 28-day mortality and clinical cure were similar between the treatment groups, and findings in the intention-to-treat (ITT) population were supported by sensitivity and per-protocol analyses.

Ceftolozane with tazobactam was generally well tolerated. However, limited safety data are available for the high dose used in this study, which is recommended for HAP and VAP. Treatment-related adverse events were more common with ceftolozane with tazobactam than with meropenem (11% [38 of 361] compared with 8% [27 of 359] respectively; no statistical analysis). The most commonly reported treatment-related adverse events with ceftolozane with tazobactam were abnormal liver function tests, Clostridioides difficile (formerly known as Clostridium difficile) colitis and diarrhoea.

Likely place in therapy

The manufacturer of ceftolozane with tazobactam (Merck Sharp & Dohme Limited) anticipates that it will be used in line with good antimicrobial stewardship, on the advice of a microbiologist, to treat critically ill ventilated adults with HAP and VAP, who are

deteriorating or not responding to initial antibiotic therapy, and who have confirmed or highly suspected Pseudomonas aeruginosa.

Specialists involved in producing this evidence summary consider that ceftolozane with tazobactam provides a potentially useful alternative for treating some adults with HAP and VAP who have limited treatment options because they have infections suspected or proven to be caused by caused by Enterobacterales (excluding carbapenem-resistant bacteria) or multidrug-resistant Pseudomonas aeruginosa. Local antibiotic resistance patterns will need to be taken into account.

Factors for decision making

Effectiveness

ASPECT-NP was a multicentre randomised controlled, double-blind, non-inferiority trial. It included 726 adults (mean age 60 years) with hospital-acquired pneumonia (HAP) caused by Gram-negative pathogens, who were undergoing mechanical ventilation. Of these, 71% had ventilator-associated pneumonia (VAP) and 29% had HAP that had worsened and needed mechanical ventilation (ventilated HAP). Participants were randomised to receive ceftolozane with tazobactam 2 g/1 g or meropenem 1 g intravenously every 8 hours for 8 to 14 days. The primary outcome reported was 28-day all-cause mortality (the FDA primary outcome) and the key secondary outcome was clinical cure at the test-of-cure visit (7 to 14 days after the end of treatment: the EMA primary outcome). Clinical cure was defined as resolution of baseline signs and symptoms of HAP, with no new signs or symptoms and no need for additional antibiotic treatment.

Mortality

At 28 days, 24.0% (87 of 362) of participants in the ceftolozane with tazobactam group had died compared with 25.3% (92 of 364) of participants in the meropenem group (intention-to-treat [ITT] population; weighted treatment difference 1.1%, 95% confidence interval [CI] -5.1% to 7.4%). The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of -10%, showing that ceftolozane with tazobactam was statistically non-inferior to meropenem. Sensitivity analyses support this result (Zerbaxa EPAR - Assessment report - variation).

Clinical cure

At the test-of-cure visit, 54.4% (197 of 362) of participants in the ceftolozane with tazobactam group experienced clinical cure compared with 53.3% (194 of 364) of participants in the meropenem group (ITT population; weighted treatment difference 1.1%, 95% CI -6.2 to 8.3). The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of -12.5%, showing that ceftolozane with tazobactam was statistically non-inferior to meropenem. A per-protocol analysis in the clinically evaluable population supports this result.

Microbiological eradication

In the microbiological ITT population (participants who received at least 1 dose of study treatment and from whom at least 1 Gram-negative or streptococcal respiratory pathogen susceptible to at least 1 study treatment was cultured from baseline lower respiratory tract samples; n=511), the most commonly identified lower respiratory tract pathogens were Enterobacterales (usually Klebsiella pneumoniae and Escherichia coli), which were isolated in 74% (380 of 511) of participants, and Pseudomonas aeruginosa, which was isolated in 25% (128 of 511) of participants. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales were isolated from 31% (157 of 511) of participants.

Ceftolozane with tazobactam and meropenem appeared to be similar in terms of microbiological eradication in the microbiological ITT population. However, this was a secondary outcome that was not statistically powered for non-inferiority testing.

Only 3% of baseline isolates of Pseudomonas aeruginosa were resistant to ceftolozane with tazobactam, whereas 13% were resistant to meropenem. By contrast, around a third of isolates of ESBL-producing Enterobacterales were resistant to ceftolozane with tazobactam but none were resistant to meropenem. Despite the differences in susceptibility profiles, subgroup analyses based on causative pathogens suggested that clinical outcomes were similar between the ceftolozane with tazobactam and meropenem groups. However, these subgroup analyses were not statistically powered for comparison.

Safety

In the ASPECT-NP trial, treatment-related adverse events were reported by 11% (38 of 361) of participants using ceftolozane with tazobactam and 8% (27 of 359) of participants using meropenem (no statistical analysis). Serious adverse events were also more common

with ceftolozane with tazobactam than with meropenem (2% [8 of 361] compared with 1% [2 of 359] respectively; no statistical analysis).

Study treatment was discontinued because of treatment-related adverse events in 1% of participants in both groups (4 of 361 using ceftolozane with tazobactam and 5 of 359 using meropenem). Study treatment was discontinued because of insufficient therapeutic effects in 6% (23 of 361) of participants in the ceftolozane with tazobactam group and 4% (15 of 359) of participants in the meropenem group (no statistical analyses). No deaths in either group were considered related to study treatment.

The summary of product characteristics states that the most common adverse effects (at least 3 in 100) seen in phase 3 trials assessing ceftolozane with tazobactam for all licensed indications were nausea, headache, constipation, diarrhoea, pyrexia and raised liver enzymes. These were generally considered mild or moderate in severity.

Limitations of the evidence

ASPECT-NP was a relatively large, well-designed and reported study, which was undertaken in accordance with regulatory requirements. All study participants were mechanically ventilated and critically ill; therefore, it is unclear whether the study results are applicable to people with less severe HAP without intubation. The study excluded people with immunosuppression and cystic fibrosis, and people receiving dialysis. Adults only were included and ceftolozane with tazobactam is not currently licensed for treating children and young people.

To ensure a high concentration in the lungs of the seriously ill people in the study, the dose of ceftolozane with tazobactam used (and subsequently licensed for HAP and VAP) was double that recommended for other indications (2 g/1 g compared with 1 g/0.5 g for complicated urinary tract infections and complicated intra-abdominal infections; summary of product characteristics). According to some reports, higher doses of meropenem may have been preferable as the comparator (2 g 8 hourly over 3 hours for equivalent antibacterial activity to high-dose ceftolozane with tazobactam; Kalil and Zavascki 2019 and Frippiat et al. 2014). This suggests that the study may have underestimated the efficacy of meropenem. However, although specialists advised that high doses of meropenem are sometimes used for HAP and VAP in the UK, standard doses (as used in the study) are generally preferred.

Ceftolozane with tazobactam is a relatively new antibiotic, which is generally not used first

line. Therefore, data on resistance and the impact in clinical practice in the UK are limited. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018 to 2019 states that monitoring the use of new antibiotics and detecting emerging resistance to these medicines is a crucial component of antimicrobial usage surveillance to inform antimicrobial stewardship activities and preserve treatment effectiveness. Although susceptibility testing for ceftolozane with tazobactam is currently uncommon and selective (following resistance to first- and second-line antibiotics), resistance has nonetheless been recorded.

Person-related factors

Ceftolozane with tazobactam is administered by intravenous (IV) infusion over 1 hour, every 8 hours. In practice, it is highly likely it will be prescribed and administered in a hospital setting.

Resource implications

The acquisition cost of ceftolozane with tazobactam is £67.03 (excluding VAT) per vial, meaning the cost of 1 day's treatment at the usual dosage for HAP and VAP (2 g/1 g [2 vials] every 8 hours) is £402.18 (BNF, November 2019).

The acquisition costs (excluding VAT) of many other IV antibiotics that are used for HAP and VAP (caused or suspected to be caused by Gram-negative pathogens) are lower than that of ceftolozane with tazobactam. The acquisition cost of meropenem alone is £17.78 (excluding VAT) for 1 vial containing 1 g of powder for solution for injection (Drug Tariff, November 2019). The cost of 1 day's treatment with 2 g (2 vials) every 8 hours is £106.68.

The manufacturer estimates that usage of ceftolozane with tazobactam will be low, reflecting its anticipated positioning following confirmed susceptibility testing. Usage should be under the guidance of an appropriately experienced infection specialist (such as a clinical microbiologist or infectious diseases consultant), following the principles of good antimicrobial stewardship.

Depending on the proven pathogens contributing to the infection, ceftolozane with tazobactam may need to be given in combination with other antimicrobials for which additional treatment costs would need to be considered.

See the full evidence review for more information.

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