NICE National Institute for Health and Care Excellence

NICE advice

Antimicrobial prescribing: imipenem with cilastatin and relebactam

Evidence summary
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Product overview

The content of this evidence summary was up-to-date in October 2020. 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.

Imipenem with cilastatin and relebactam (Recarbrio, Merck Sharp & Dohme B.V) is given intravenously and is a combination of a broad-spectrum carbapenem antibiotic (imipenem); an inhibitor of dehydropeptidase-I, the renal enzyme that metabolises and inactivates imipenem (cilastatin); and a beta-lactamase inhibitor (relebactam). Only imipenem has antibacterial activity. Imipenem with cilastatin and relebactam has a marketing authorisation for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options.

Advisory statement on likely place in therapy

Imipenem with cilastatin and relebactam may be an option for treating infections due to gram-negative aerobic organisms in adults with limited treatment options, particularly when other antimicrobials have failed. Take account of local antimicrobial resistance and seek specialist microbiological advice. Follow recommendations on new antimicrobials in the NICE guideline on antimicrobial stewardship.

Rationale

The European public assessment report for imipenem with cilastatin and relebactam states that there is still a high unmet clinical need for additional antimicrobials addressing carbapenem resistance in gram-negative organisms.

Evidence from 2 phase 3 randomised controlled trials in around 600 people treated in a non-UK hospital setting suggests that the efficacy of imipenem and cilastatin with relebactam was similar (no planned statistical analysis) to colistin plus imipenem for treating imipenem non-susceptible pathogens, and non-inferior to piperacillin with tazobactam for treating susceptible pathogens. Imipenem and cilastatin with relebactam has not been compared with other treatments.

The infections treated in the studies were hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection and complicated urinary tract infection (UTI) in adults. There is no evidence for treating other infections with limited treatment options.

In both studies, participants had no response to previous antimicrobial treatment before receiving imipenem and cilastatin with relebactam. Therefore, it may be an option for people with limited treatment options who have serious infections suspected or proven to be caused by multi-drug resistant aerobic gram-negative bacteria according to its licensed indications. The daily cost of imipenem and cilastatin with relebactam is £614.20 at the usual dose (1 vial [500 mg/500 mg/250 mg] every 6 hours).

Imipenem with cilastatin has been combined with relebactam to overcome carbapenem resistance. Local antimicrobial resistance patterns and trends need to be considered because imipenem with cilastatin and relebactam may not be appropriate in areas where

class B enzymes and class D carbapenemase resistance is common.

The NICE guideline on antimicrobial stewardship makes recommendations on the effective use of new antimicrobials. Imipenem and cilastatin with relebactam should be reserved for those people most likely to benefit from their use, following specialist microbiological advice to help monitor use and limit antimicrobial resistance.

Factors for decision making

Effectiveness and safety

Evidence was from 2 phase 3 randomised controlled trials (Motsch et al. 2020 and Titov et al. 2020) both conducted in a non-UK hospital setting. Motsch et al. (2020; n=47) compared imipenem with cilastatin and relebactam with colistin plus imipenem with cilastatin in adults with hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection and complicated urinary tract infection (UTI) with imipenem non-susceptible pathogens. It is difficult to draw firm conclusions from this study as there was no formal statistical analysis (except for nephrotoxicity). Titov et al. (2020; n=537) is a larger study that compared imipenem with cilastatin and relebactam with piperacillin with tazobactam in adults with bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia) caused by treatment-susceptible pathogens.

In the study by Motsch et al. (2020), overall response (primary outcome) was 71.4% in the imipenem with cilastatin and relebactam group compared with 70.0% in the colistin plus imipenem with cilastatin group. This outcome measure was defined as: bacterial pneumonia, 28-day all-cause mortality; complicated intra-abdominal infection, day 28 clinical response; and complicated UTI, composite clinical and microbiologic response at early follow up.

In the study by Titov et al. (2020), imipenem with cilastatin and relebactam was non-inferior to piperacillin with tazobactam for day 28 all-cause mortality (primary outcome, 15.9% versus 21.3% respectively, adjusted treatment difference -5.3%, 95% confidence interval [CI] -11.9 to 1.2, non-inferiority $p<0.001$) and favourable clinical response (resolution of baseline bacterial signs and symptoms and no non-study antibacterial treatment for bacterial pneumonia) at early follow up (61.0% versus 55.8% respectively, adjusted treatment difference 5.0% 95% CI -3.2 to 13.2, non-inferiority $p<0.001$).

In Motsch et al. (2020), serious adverse events occurred in 9.7% of total participants in the imipenem with cilastatin and relebactam group and 31.3% of total participants in the colistin plus imipenem with cilastatin group; none were considered related to the study treatment. In Titov et al. (2020), 26.7% of the imipenem with cilastatin and relebactam group experienced serious adverse events compared with 32.0% in the piperacillin with tazobactam group (1.1% and 0.7% were considered related to study treatment, respectively).

Treatment-emergent nephrotoxicity was statistically significantly lower in the imipenem with cilastatin and relebactam group compared with the colistin plus imipenem with cilastatin group (Motsch et al. 2020).

The summary of product characteristics for Recarbrio reports common adverse reactions (frequency 1 to 10 per 100) as diarrhoea, nausea, vomiting, increased alanine aminotransferase and aspartate aminotransferase. *Clostridioides difficile*-associated diarrhoea has also been reported with treatment.

Limitations of the evidence

The evidence for using imipenem with cilastatin and relebactam for treating patients with limited treatment options is limited to 2 studies. Imipenem with cilastatin and relebactam has been compared only with colistin plus imipenem with cilastatin, and piperacillin with tazobactam, so it is uncertain how its effectiveness and safety compares with other antimicrobial treatments. Effectiveness and safety data are limited to bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection and complicated UTI. No participants were enrolled from the UK, further limiting the generalisability of the results to UK practice.

Motsch et al. (2020) is limited by its small study size, and it is difficult to draw firm conclusions from it because of its non-inferential descriptive study design. Relatively few participants with carbapenem-resistant Enterobacterales infection and complicated intra-abdominal infection were enrolled. Titov et al. (2020) was a larger study but is limited to pathogens that were susceptible to the study treatment and effectiveness and safety in carbapenem-resistant pathogens was not assessed.

Person-centred factors

Imipenem with cilastatin and relebactam is administered by intravenous infusion over 30 minutes, every 6 hours, and is likely to be used in a hospital setting.

Antimicrobial resistance

Imipenem with cilastatin and relebactam is a new antimicrobial and therefore data on resistance and impact on clinical practice in the UK are limited. Information on resistance can be found on Public Health England antimicrobial resistance local indicators.

According to the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2018 to 2019, class B enzymes and class D carbapenemases accounted for approximately 84% of carbapenemase-resistant Enterobacterale isolates in 2018. Relebactam does not inhibit class B enzymes or D carbapenemases. Therefore, imipenem with cilastatin and relebactam should not be considered for infections caused by these class B enzymes or D carbapenemases.

Resource implications

Imipenem with cilastatin and relebactam costs £153.55 per vial (NHS Specialist Pharmacy Service).

The cost of 1 day's treatment at the usual dose (1 vial [500 mg/500 mg/250 mg] every 6 hours) is £614.20.

See the full evidence review for more information.

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