NICE advice

Antimicrobial prescribing: eravacycline for complicated intra-abdominal infections in adults

Evidence summary
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Product overview

The content of this evidence summary was up to date in March 2022. 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.

Eravacycline (Xerava, PAION Deutschland GmbH) is a tetracycline antibiotic given intravenously. It has a marketing authorisation for treating complicated intra-abdominal infections in adults.

Advisory statement on likely place in therapy

Eravacycline may be an option for treating complicated intra-abdominal infections in adults with limited treatment options when standard intravenous antibiotics are not suitable or have been ineffective. 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 (EPAR) on eravacycline states that complicated intra-abdominal infections are the second most common cause of morbidity and mortality, after pneumonia in adults, in the intensive care unit. They are characterised by an increased mortality because of both the underlying patient health status and the increased likelihood of infection caused by multi-drug resistant organisms. The pathogens most frequently seen in complicated intra-abdominal infections include the Gram-negative bacteria *Escherichia coli* and other common *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Bacteroides fragilis*. Second or third generation cephalosporins in combination with metronidazole; beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors; and carbapenems are commonly used for treating complicated intra-abdominal infections. Effective management of complicated intra-abdominal infection requires early diagnosis, appropriate surgical intervention and empiric, broad-spectrum antimicrobial treatment.

Evidence from 2 phase 3 randomised controlled trials in non-UK hospitals (n=541 and n=500) found that eravacycline was non-inferior to either ertapenem or meropenem for treating complicated intra-abdominal infections in adults. Eravacycline was administered every 12 hours. Treatment duration was a minimum of four 24-hour dosing cycles. The infections treated in the studies were complicated intra-abdominal infections which included complicated appendicitis, cholecystitis, gastric perforation and peritonitis.

Increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem (EPAR report). Eravacycline offers an alternative for treating complicated intra-abdominal infections.

The NICE guideline on antimicrobial stewardship makes recommendations on the effective use of new antimicrobials. Eravacycline should be reserved for those people most likely to benefit from it, after specialist microbiological advice to help monitor use and limit antimicrobial resistance.

Factors for decision making

Effectiveness and safety

Evidence was from 2 multicentre, randomised, double-blind phase 3 studies (Solomkin et al. [2017] and Solomkin et al. [2019]) in people with complicated intra-abdominal infections, such as acute

appendicitis. Solomkin et al. (2017; n=541) compared intravenous eravacycline with intravenous ertapenem and Solomkin et al. (2019; n=500) compared intravenous eravacycline with intravenous meropenem. The 2 studies found that eravacycline was non-inferior to either ertapenem or meropenem for the primary endpoint, clinical response at the test-of-cure visit. The primary end point, the clinical response at the test-of-cure visit in the modified intention to treat population, was categorised as clinical cure, clinical failure or unknown. Solomkin et al. (2017) found that 87.0% of people in the eravacycline arm and 88.8% of people in the ertapenem arm met the requirements of clinical cure at the test-of-cure visit. Solomkin et al. (2019) found that 92.4% of people in the eravacycline arm and 91.6% of people in the meropenem arm met the requirements of clinical cure at the test-of-cure visit.

Eravacycline was also found to be non-inferior to ertapenem and meropenem for the secondary endpoints such as clinical cure at the test-of-cure visit in the micro-intention-to-treat and clinically evaluable population.

The summary of product characteristics (SPC) for eravacycline gives the common adverse reactions (seen in between 1 in 10 and 1 in 100 people) as thrombophlebitis, phlebitis, nausea, vomiting and infusion site reactions.

Adverse events were seen in 113/270 (41.9%) of participants given eravacycline and 75/268 (28%) of participants given ertapenem (Solomkin et al. 2017). In Solomkin et al. (2019) treatment-emergent adverse events were seen in 93/250 (37.2%) of participants given eravacycline and 77/249 (30.9%) of participants given meropenem.

Limitations of the evidence

Solomkin et al. (2017) and Solomkin et al. (2019) were well-conducted randomised controlled trials. The participants included in the studies were mostly 65 years or younger and of white ethnicity and had a reported APACHE II (a mortality prediction tool based on 12 routine physiologic measurements; range 0 to 71; lower scores are better) mean score of 6.7. Therefore, the populations may not be representative of people who are likely to be at higher risk of dying with higher APACHE II scores. Solomkin et al. (2017) and Solomkin et al. (2019) compared eravacycline with either ertapenem or meropenem, which are both currently used in practice to treat complicated intra-abdominal infections.

Both studies met the pre-specified upper limit of patients randomised with complicated appendicitis. This was set at 50% in Solomkin et. al (2019) and 30% in the Solomkin et al. (2017) study. However, the 50% limit set by Solomkin et al. (2019) was not in line with the practice advised

by the Committee for Medicinal Products for Human Use, which states that the percentage of patients with complicated appendicitis should be limited to 30%. It is not known if this would have had an impact on the results.

Person-centred factors

Eravacycline is given by intravenous infusion only, over approximately 1 hour. The recommended dose is 1 mg/kg eravacycline every 12 hours for 4 to 14 days. In practice, it is likely to be given in a hospital setting.

Specialists who commentated on this evidence review highlighted that in practice eravacycline is likely to be prescribed for people who are allergic to penicillin or when standard intravenous antibiotics are not suitable or have been ineffective.

Eravacycline has a marketing authorisation for treating adults only and there is no requirement to adjust the dose for age, weight, or mild to moderate renal function.

Antimicrobial resistance

Eravacycline is a new antimicrobial and therefore data on resistance and impact on clinical practice in the UK is limited. Information on resistance can be found on UK Health Security Agency antimicrobial resistance local indicators.

Resistance to eravacycline has been seen in *Enterococcus* harbouring mutations in the rpsJ gene. There is no target-based cross-resistance between eravacycline and other classes of antibiotics such as quinolones, penicillins, cephalosporins and carbapenems. Other bacterial resistance mechanisms that could potentially affect eravacycline are associated with upregulated, non-specific intrinsic multidrug-resistant efflux (SPC).

Resource implications

The cost of eravacycline 100 mg powder for concentrate for solution for infusion is £105 for 1 vial (see MIMS, May 2022). The cost of a treatment course based on an average weight of 75 kg and assuming part vials are not stored or shared is £840 to £2,940 for 4 to 14 days, respectively.

In comparison, the cost of ertapenem 1g powder for solution for infusion in March 2022 was £31.65 for 1 vial (see the Drug Tariff). The cost of a treatment course for 4 to 14 days is £127 to £443.

The cost of meropenem 1g powder for solution for injection in March 2022 was £20.38 for 1 vial (see the Drug Tariff). The cost of a treatment course for 4 to 14 days is £245 to £856.

This cost is for the medicine only and does not include any associated costs related to antibiotic administration in hospital.

See the full evidence review for more information.

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