AWMSG Secretariat Assessment Report – Limited submission

Cefepime (as dihydrochloride monohydrate) (Renapime®) 1 g and 2 g powder for solution for injection or infusion

Company: Renascience Pharma Ltd

Licensed indication under consideration: Treatment of infections caused by bacteria that are cefepime-sensitive: lower respiratory tract infections, including nosocomial pneumonia and community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and secondary bacterial infection of acute bronchitis; uncomplicated and complicated urinary tract infections, including pyelonephritis; skin and subcutaneous infections; intra-abdominal infections, including peritonitis and biliary tract infections; gynaecological infections; bacterial meningitis in infants and children; in combination with other antibacterial agents in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection; treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The applicant company suggests that use of cefepime should be considered in a subgroup of patients, within its licensed indication, who have *pseudomonas* infections where first-line agents are not effective or are contraindicated.

Marketing authorisation date: 8 December 2017

Comparators

The comparators included in the company's submission are:

- Ceftolozane/tazobactam
- Ceftaroline fosamil
- Ceftazidime/avibactam.

Limited submission details

- Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

Clinical effectiveness

- Cefepime is a fourth-generation broad-spectrum cephalosporin. The Medicines and Healthcare products Regulatory Agency (MHRA) approved cefepime in December 2017 via the decentralised procedure. Cefepime has been widely used in Europe and has established efficacy and tolerability.
- AWTTC-sought clinical expert opinion suggests that cefepime is likely to be reserved for use when other antibacterial agents are considered inappropriate or when alternatives have failed to demonstrate efficacy. Clinical experts highlighted that the activity of cefepime against AmpC beta-lactamase-producing organisms might be beneficial in some circumstances.
- The company submission includes nine studies comparing the efficacy and safety of cefepime to that of other antibiotics for the treatment of pneumonia, urinary tract infections, skin and surgical wounds, and pyelonephritis. Whilst the efficacy and safety of cefepime to other antibiotics was comparable, not all of them were randomised controlled trials. The applicant company provided evidence to support the use of cefepime in resistant *pseudomonas* infections where first-line agents were not effective. The study evaluated clinical isolates resistant to ceftazidime and/or cefotaxime and demonstrated a lower potential for resistance of cefepime compared to the broad-spectrum cephalosporins.
- The safety profile of cefepime is comparable to that of the reference product and to other cephalosporins. Most common adverse events, in the more than 6,400 adults treated with cefepime in clinical studies, were gastrointestinal symptoms and hypersensitivity reactions. The safety profile of cefepime in infants and children is similar to that seen in adults. No new or unexpected safety concerns arose from the MHRA's licensing procedure.
- Cefepime can be administered intramuscularly as well as intravenously, compared to the company proposed comparators that are only available via the intravenous route. There is an acknowledged rise in the levels of antibacterial resistance across Europe, and the need for new effective treatments is recognised.

Budget impact

- The applicant company estimates that 180 people annually in Wales are eligible for treatment with cefepime, based on the subpopulation of eligible patients as set out by the company.
- The estimate is based on incidence data of *pseudomonas* bacteraemia, from a Public Health England 2014 Health Protection Report, applied to Welsh population data. The company proposes that episodes of *pseudomonas* bacteraemia provides an estimated prevalence of serious *pseudomonas* infection in Wales. To estimate overall episodes of *pseudomonas* infections, the company applied a scaling factor of six. Antimicrobial resistance data produced by Public Health Wales in 2017 suggests that 21% of overall episodes are resistant to first- and second-line treatments.
- Based on uptake estimates of 11% in Year 1 and 67% in Year 5, the company estimates that the number of patients likely to receive the medicine will be 20 in Year 1, rising to 120 in Year 5.
- The company's model looks at acquisition costs only and assumes that in the scenario without cefepime being available, patients will receive either ceftazidime/avibactam, ceftolozane/tazobactam or ceftaroline fosamil seven-day courses, weighted equally across the three comparators. In the scenario in which cefepime is available, cost is based on a seven-day course at the maximum dose of 6 g per day.
- AWTTC-sought clinical expert opinion suggests that the comparators are appropriate, although they also highlight that it might not be a true representation of prescribing in Wales. There is uncertainty as to whether the choice of comparators and the proportions of patients receiving these treatments is reflective of practice in Wales. For example, ceftazidime/avibactam is not endorsed for use in Wales due to the absence of a submission from the marketing authorisation holder. There is also uncertainty related to the duration of treatment as the company has not presented evidence on which these assumptions are based.
- The company-estimated net medicine acquisition cost for cefepime is a saving of [commercial in confidence figure removed] in Year 1 and a saving of [commercial in confidence figure removed] in Year 5.
- The assumptions made regarding comparators have not been supported with evidence and, collectively, estimates of budget impact are subject to uncertainty. However, based on information provided by clinical experts in Wales, the patient numbers are likely to be small and there is likely to be a cost saving associated with the use of cefepime in place of the comparators provided by the company.

Additional information

- AWTTC is of the opinion that, if recommended, cefepime (Renapime®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.
- The company anticipates that cefepime (Renapime®) may be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 16 September 2019
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Cefepime (Renapime®) 1 g and 2 g powder for solution for injection/infusion. Reference number: 4129. October 2019.