HIGH COST DRUGS SUBGROUP

GMMMG Greater Manchester Medicines Management Group NHS

Date 10.10.19

Bezlotoxumab▼ for the prevention of recurrence of Clostridium difficile infection in adults at high risk of recurrence.

Recommendation	GMMMG does not recommend the routine commissioning of Bezlotoxumab for the prevention of recurrence of Clostridium difficile in adults at high risk of recurrence, pending updated guidance from Public Health England or NICE to support its place in therapy. It is noted that the planned NICE TA was suspended in February 2018 as the company stated it will not make a submission. The summary of product characteristics does not define high risk within the therapeutic indication, but the European public assessment report considered the following to be risk factors, based on European guidance and the population studied in the trials: • age over 65 years • history of previous C difficile infection • being immunocompromised • having infection with hypervirulent strain, including ribotype 027 • having severe C. difficile infection.
Background	Bezlotoxumab (Zinplava, Merck Sharp & Dohme Limited) is a human monoclonal antitoxin antibody that binds with high affinity to Clostridium difficile toxin B and neutralises its activity. It received a marketing authorisation in January 2017 and was launched in June 2017. The planned NICE TA has now been suspended, but the NICE evidence summary from June 2017 which has been used to produce this statement. Bezlotoxumab is indicated for preventing future episodes of diarrhoea in people who are taking antibiotics to treat their C difficile infection, and who are at high risk of the infection coming back. It is administered as a single one-off intravenous infusion during a course of antibacterial therapy for C difficile infection. PHE guidance for the management of Clostridium difficile infection (last updated May 2013) does not currently include any guidance on the use of Bezlotoxumab. After initial treatment and resolution of diarrhoea, 15% to 35% of people with C difficile infection experience recurrence. Recurrent infection is more difficult to treat and is associated with more hospitalisations, severe outcomes, and higher costs than initial episodes. Currently no medicines are licensed for preventing first episodes of C difficile infection and only bezlotoxumab is licensed for preventing the recurrence of C difficile infection in adults who are at high risk of developing this infection again.

Efficacy and Safety	Bezlotoxumab is the first medicine that is indicated for preventing the recurrence of C difficile in adults who are at high risk of developing this infection again; however, its place in therapy is currently unclear. Bezlotoxumab was generally well-tolerated in the trials and had a similar adverse effect profile to placebo. Common adverse effects seen in the bezlotoxumab group in the trials (in more than 4 in 100 participants) included abdominal pain, diarrhoea, nausea, pyrexia, urinary tract infection and headache. In pooled analyses of MODIFY I and MODIFY II, at 12 weeks, recurrence of C difficile infection and sustained clinical cure were each improved by about 10% in absolute terms with a single infusion of bezlotoxumab 10 mg/kg compared with placebo in adults with confirmed primary or recurrent C difficile infection who were receiving oral standard-of-care antibiotics (both statistically significant: numbers needed to treat [NNT] 10 and 11 respectively). However, almost three quarters of people given placebo did not have recurrent infection by week 12 (73% compared with 83% with bezlotoxumab), and around half had sustained cure (54% compared with 64% with bezlotoxumab). Conversely, almost a fifth of people given bezlotoxumab had recurrent infection and more than a third did not have sustained cure (17% and 36% respectively compared with 27% and 46% respectively with placebo). Compared with the total trial population, the NNTs for preventing recurrent infection at 12 weeks were lower in people aged 65 years or more, with previous C difficile infection in the last 6 months, who were immunocompromised, or who had severe infection (NNTs 7, 7, 8 and 9 respectively), reflecting the licensed indication, which specifies use in high risk subgroups. This was not the case for people with hypervirulent strains, in whom no significant difference was seen compared with placebo.
Cost Effectiveness/ Affordability	Bezlotoxumab is administered as a single, one-off intravenous infusion given over 60 minutes. It is administered alongside an antibiotic for treating the current episode of C difficile infection. There is no experience of repeat administration of bezlotoxumab. The NHS List Price for 1 x 1000mg vial of bezlotoxumab 1,000 mg is £2,470.00. The dose of bezlotoxumab is 10 mg/kg; therefore, more than 1 vial will be needed to treat people weighing more than 100 kg. The manufacturer (Merck Sharp & Dohme Limited) anticipates that bezlotoxumab will be used according to the licensed indication under the guidance of a microbiologist or infectious disease specialist, following the principles of good antimicrobial stewardship. Merck Sharp & Dohme Limited anticipates that usage will be appropriately low, with an estimated peak of 700 eligible people being treated with bezlotoxumab in a 12-month period after 5 years. This reflects the indication in adults at high-risk of recurrence of C difficile infection, in line with local unmet need. This figure represents an estimation based on current epidemiology; a significant increase in C difficile infection or recurrence would have a large impact on these figures (source: Merck Sharp & Dohme Limited, March 2017). (NICE ES13)
Monitoring	Where Blueteq has been introduced to the trust as part of the contractual arrangements, a form should be completed and on-going funding approval will be made by meeting the criteria outlined on completion and submission of a Blueteq form.
Patient perspective	In the absence of an agreed GM wide commissioning position for the use of this agent, patient access to this agent will be restricted to application via IFR

References

- Updated guidance on the management and treatment of Clostridium difficile infection. May 2013. Public Health England https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/321891/Clostridium_difficile_management_and_treatment.pdf

- NICE Evidence summary [ES13] Preventing recurrence of Clostridium difficile infection: bezlotoxumab. Published date: June 2017 https://www.nice.org.uk/advice/es13/chapter/Key-points