Bezlotoxumab ZINPLAVA®
Criteria for Use
November 2017

VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive bezlotoxumab without local adjudication.*

☐ Patient with fulminant CDI (e.g. life-threatening CDI or toxic mega-colon)
☐ Known hypersensitivity to bezlotoxumab
☐ Patient with a history of congestive heart failure unless the benefit is felt to outweigh the risk (see issues for consideration)

Inclusion Criteria *The answers to ALL OF THE FOLLOWING must be fulfilled in order to meet criteria.*

☐ Patient receiving standard therapy for *C.difficile* infection (CDI) with oral vancomycin, metronidazole or fidaxomicin
☐ Patient with documented CDI with both diarrhea (at least 3 loose stools in a 24 hour period) in addition to a positive *C .difficile* toxin test in the past 7 days
☐ Recurrence of CDI with prior receipt of 2 or more completed courses of oral vancomycin including a tapered or pulse regimen or fidaxomicin within the prior 6 months

NOTE: If metronidazole used for initial episode, a standard course of oral vancomycin can be used for first recurrence. If oral vancomycin used for initial episode, oral vancomycin with a tapered and/or pulse regimen should be used for first recurrence (rather than a second standard 10-day course of vancomycin)

☐ Patient currently hospitalized or eligible to receive the infusion in an ambulatory infusion clinic

Dosage and Administration

10 mg/kg (based on actual body weight) in 250 ml NS or D5W as an intravenous infusion over 60 minutes

Note volume can be decreased to 200 ml in patients where volume is a concern. Should be administered with a 5 micron or smaller in line or add-in filter. Bezlotoxumab can be given via peripheral or central venous catheter

Issues for Consideration

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- Inflammatory bowel disease: Certain patients were excluded from MODIFY I and II due to potential confounding impact on clinical or laboratory endpoints. These included patients with chronic diarrheal illness, such as Ulcerative colitis or Crohn's disease. As they were excluded, the efficacy benefit of bezlotoxumab in these patients is not known, and use in these patients should be on a case by case basis, ideally in conjunction with a Gastroenterologist knowledgeable in the management of inflammatory bowel disease.

- Historical congestive heart failure (CHF): In the two Phase 3 trials, MODIFY I and II, CHF was reported in 2.3% of bezlotoxumab patients and 0.9% of placebo patients during the 12 week study period. In particular, in the subgroup of patients with a history of CHF, serious adverse events were reported in 12.7% of bezlotoxumab patients as compared with 4.8% of placebo treated patients. In addition, there were more deaths in the bezlotoxumab treated patients with a history of CHF (19.5%) versus those treated with placebo (12.5%). Bezlotoxumab should only be used in patients with a history of CHF when the benefit is thought to outweigh the risks.

- Only a small number of patients (4% of the total) in the Phase 3 trials received fidaxomicin as their specific CDI therapy. It is unknown whether bezlotoxumab will provide similar reductions in relapse when used with fidaxomicin, or how bezlotoxumab compares with fidaxomicin directly for reducing relapse as most patients received either vancomycin or metronidazole with bezlotoxumab. Consideration should be given to using bezlotoxumab with standard CDI therapy including metronidazole or vancomycin until further data on use with fidaxomicin is available.

- Pregnancy and/or breastfeeding: patients who were pregnant or breastfeeding were excluded from MODIFY I and II. In addition, given the long half-life of bezlotoxumab (approximately 19 days), subjects had to agree to adequate contraception during the 12 week study period. There is no data on the safety of bezlotoxumab in pregnancy or whether it passes into human breast-milk.

Other issues for consideration

- Patients with a life-expectency of less than 72 hours were excluded from MODIFY I and II. These patients are unlikely to benefit from therapy with bezlotoxumab and therapy in this population should generally be discouraged

- The use of antiperistaltic agents (or planned use during the 14 day study period) was an exclusion criterion due to the possible confounding effect on the clinical endpoint of diarrhea. In general, antiperistaltic agents should be avoided in patients with CDI when possible, particularly during the 14 days after infusion. Receipt of immune globulin in the 6 months prior to randomization was also an exclusion criterion as this would confound the laboratory endpoint of anti-toxin A and B antibodies. As bezlotoxumab is also a human antibody, it is unclear whether the safety or efficacy is different in someone who has received immune globulin.

- Given the long half-life of bezlotoxumab, providers should consider recommending patients not donate blood or blood products for 12 weeks as the safety of blood products in patients who have received bezlotoxumab is unknown.

- Infusion related reactions were reported in 10% of bezlotoxumab and 8% of placebo treated patients on the day of or after infusion. Patients should be monitored during infusion for signs and symptoms of severe infusion related reaction such as nausea, fever, dizziness, dyspnea or hypotension.

- Adequate infection control practices are crucial to prevention of the spread of CDI and should be utilized in all patients receiving bezlotoxumab.

References

1. ZINPLAVA [package insert]. Merck and Co., October 2016. Accessed September 27, 2017
2. ZINPLAVA FDA Medical Review, Application number 761046. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761046Orig1s000MedR.pdf . Accessed September 27, 2017
3. Wilcox MH, Girding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *C.difficile* Infection. N Engl J Med 2017;376(4):305-17.
4. Lowy I, Molrine D, Leav B, et. al., Treatment with monoclonal antibodies against *Clostridium difficile* toxins. New Engl J Med 2010;362(3):197-205.