Bezlotoxumab (Zinplava) for Prevention of Recurrent Clostridium Difficile Infection .......... p 49

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Bezlotoxumab (Zinplava) for Prevention of Recurrent Clostridium difficile Infection

The FDA has approved the fully human monoclonal antibody bezlotoxumab (Zinplava – Merck) for use with antibacterial drug treatment to reduce recurrence of Clostridium difficile infection (CDI) in adults with CDI at high risk for recurrence. It is the first drug to be approved for this indication.

Pronunciation Key
Bezlotoxumab: bez’ loe tox’ ue mab  Zinplava: zin plah’ va

CDI – CDI is the most common infectious cause of healthcare-associated diarrhea in adults. The incidence and severity of CDI have increased in recent years with the emergence of an epidemic hypervirulent strain (NAP1/B1/027).¹ The recurrence rate after an initial episode of CDI is typically 20-25%. Patients who develop one recurrent episode have up to a 35% chance of having another one, and patients with at least three CDI episodes have up to a 65% chance of additional recurrences.²

STANDARD TREATMENT – Oral metronidazole (Flagyl, and generics) and oral vancomycin (Vancocin, and generics) have been the drugs of choice for treatment of an initial episode of CDI for several years. Recent data suggest that oral vancomycin is more effective than oral metronidazole in preventing death in patients with CDI.³ Fidaxomicin (Dificid) appears to be at least as effective as oral vancomycin for first-line treatment of CDI with fewer recurrences in patients not infected with the hypervirulent strain.⁴⁵

Fecal microbiota transplantation (FMT) is an investigational therapy that has been highly effective in treating CDI and preventing recurrences. It is generally used only in patients with severe, refractory CDI or in those who have had multiple recurrences. More data from randomized, controlled trials are needed and its long-term safety is unknown.⁶ One randomized, open-label trial found that oral vancomycin followed by FMT was not more effective than tapered oral vancomycin alone in reducing recurrent CDI.⁷

MECHANISM OF ACTION – Pathogenic strains of C. difficile can express two exotoxins, A and/or B. These toxins damage the epithelial cells of the gut wall, resulting in an increase in gut wall permeability and induction of an acute inflammatory response.⁸ Toxin B is more virulent than toxin A. Bezlotoxumab binds to and neutralizes C. difficile toxin B. It does not bind to toxin A.

Table 1. Pharmacology

<table>
<thead>
<tr>
<th>Formulation</th>
<th>1000 mg/40 mL vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>IV infusion</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Protein catabolism</td>
</tr>
<tr>
<td>Half-life</td>
<td>19 days</td>
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CLINICAL STUDIES – Approval of bezlotoxumab was based on the results of two randomized, double-blind, placebo-controlled trials (MODIFY I and II) in 1554 adults with a positive stool test for toxigenic C. difficile.⁹ MODIFY I included some patients who were treated with actoxumab, a drug that neutralizes toxin A, and both trials included groups that were treated with actoxumab in combination with bezlotoxumab. Actoxumab alone was not effective, and the drug did not provide any additional benefit when used with bezlotoxumab.

A majority (77%) of the patients in the trials had one or more risk factor for CDI recurrence; these included: age ≥65 years, ≥1 previous CDI episode, immunosuppression, clinically severe CDI at study entry, infection with a hypervirulent strain, use of other antibacterial drugs during or after standard CDI therapy, and renal impairment. A single infusion of bezlotoxumab 10 mg/kg or placebo was administered to patients receiving 10-14 days of treatment with metronidazole, vancomycin, or fidaxomicin.

A clinical cure of the initial episode of CDI occurred in about 80% of patients treated with bezlotoxumab or placebo in the two trials. The CDI recurrence rate (new episode following initial clinical cure within 12 weeks after infusion of bezlotoxumab or placebo) in patients who started CDI antibacterial therapy before or within one day after receiving a study infusion was significantly lower with bezlotoxumab than with placebo (22% vs 33% in MODIFY I and 19% vs 33% in MODIFY II). The
incidence of sustained cure through 12 weeks after infusion was significantly higher with bezlotoxumab than with placebo in MODIFY II (67% vs 52%), but not in MODIFY I (60% vs 55%). The efficacy of bezlotoxumab was not affected by the choice of antibacterial therapy. A post-hoc analysis of European inpatients enrolled in the trials found that the rate of CDI-associated hospital readmissions within 30 days following discharge was lower in those treated with bezlotoxumab than in those who received placebo (4.5% vs 13.3%).

CONCLUSION — A single IV infusion of bezlotoxumab (Zinplava) in combination with standard antibacterial therapy significantly reduced post-treatment recurrence of Clostridium difficile infection (CDI). Use of bezlotoxumab in patients with a history of heart failure may increase the risk of heart failure and death.

ADVERSE EFFECTS — Nausea, pyrexia, and headache were the most common adverse effects of bezlotoxumab reported within 4 weeks of infusion and more often than with placebo. Infusion-related reactions reported in 1-3% of patients treated with bezlotoxumab included nausea, fatigue, pyrexia, dizziness, dyspea, headache, and hypertension. In patients with a history of congestive heart failure, use of bezlotoxumab was associated with higher rates of heart failure (12.7% vs 4.8% with placebo) and death (19.5% vs 12.5% with placebo). Overall rates of death among patients treated with bezlotoxumab or placebo were similar (7.1% and 7.5%).

PREGNANCY — Bezlotoxumab has not been studied in pregnant women or animals.

IMMUNOGENICITY — None of the patients who received bezlotoxumab in the clinical trials tested positive for anti-drug antibodies after completing treatment.

DOSAGE, ADMINISTRATION AND COST — Zinplava is available in 40-mL single-dose vials containing 1000 mg of bezlotoxumab. Prior to administration, the solution must be diluted in 0.9% sodium chloride or 5% dextrose to a final concentration of 1-10 mg/mL. Bezlotoxumab must be administered during antibacterial treatment of CDI. The recommended dosage is 10 mg/kg IV infused once over 60 minutes. The cost for one vial is $3800.11

1. I See et al. NAP1 strain type predicts outcomes from Clostridium difficile infection. Clin Infect Dis 2014; 58:1394.
11. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. March 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.