Formulary Drug Reviews

Bezlotoxumab

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Regimen Name:	Bezlotoxumab
Proprietary Name:	Zinplava (Merck)
Approval Rating:	BLA
Therapeutic Class:	Monoclonal antibodies
Similar Drugs:	None
Sound- or Look-Alike	
Names:	Actoxumab, Bicalutamide, Brodalumab

INDICATIONS

Bezlotoxumab (MK-6072) is approved by the US Food and Drug Administration (FDA) to reduce the recurrence of *Clostridium difficile* infection in patients 18 years or older receiving antibacterial drug treatment for *C. difficile* infection and at high risk for *C. difficile* infection recurrence.^{1,2} Bezlotoxumab is not indicated for the treatment of *C. difficile* infection and is not a substitute for appropriate antibacterial drug treatment.²

Symptoms of *C. difficile* infection generally include diarrhea, fever, and inflammation of the bowel. The frequency and severity of diarrhea can decrease the patient's quality of life and lead to hospitalization. Risk factors for *C. difficile* infection include the use of clindamycin, third-generation cephalosporins, penicillins, or fluoroquinolones; use

of multiple antimicrobials; prolonged antimicrobial therapy; age older than 65 years; and lower quality of health.³⁻⁹ Recurrence following treatment, due to relapse or reinfection, is a major challenge in managing *C. difficile* diarrhea.^{6,7,9}

CLINICAL PHARMACOLOGY

The gastrointestinal (GI) symptoms associated with *C. difficile* infection are caused by the presence of various endotoxins (eg, toxin A [TcdA], toxin B [TcdB], *C. difficile* binary toxin). The most common contributing endotoxins are TcdA and TcdB alone or in combination. The use of an antibody to treat *C. difficile* infection is based on the concept of humoral immunity, whereby the antibody both neutralizes and clears the toxin. Early evidence indicates that the risk of *C. difficile* infection recurrence may be related to an inadequate hormonal immune response by the host; therefore, administration of neutralizing antibodies might be an effective means of treatment. Monoclonal antibodies have longer serum half-lives than basic antibodies, which allows for less frequent administration. In addition, use of a monoclonal antibody may be effective in the treatment of primary infection and the prevention of potential recurrent infections.^{4-6,9-13} In subsequent phase 2 studies evaluating the efficacy of monoclonal antibody therapy

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compared to placebo, no significant differences in severity of diarrhea during initial *C. difficile* infection, days to resolution of symptoms during the initial episode, and proportion of patients who failed therapy were observed, but there was a decrease in *C. difficile* infection recurrence. Based on these observations, the focus of phase 3 studies shifted to an evaluation of these agents for the prevention of *C. difficile* infection recurrence.^{4,9}

Actoxumab is an anti-TcdA antibody and bezlotoxumab is an anti-TcdB antibody.^{10,14-16} Bezlotoxumab selectively binds to regions within the N-terminal half of the TcdB combined repetitive oligopeptide (CROP) domain.^{2,15} Neutralization of TcdB is achieved when bezlotoxumab binds to 2 homologous sites within the CROP domain and subsequently blocks binding of TcdB to mammalian cells.¹⁵

PHARMACOKINETICS

Geometric mean clearance of bezlotoxumab is 0.317 L/day, mean volume of distribution is 7.33 L, and elimination half-life is approximately 19 days. The clearance of bezlotoxumab increases with increasing body weight; elimination is by catabolism. The use of weight-based dosing of bezlotoxumab should adequately address differences in exposure based on body weight.²

No meaningful differences in exposure to bezlotoxumab were observed based on gender, race, ethnicity, renal function, hepatic function, or the presence of comorbid conditions.²

COMPARATIVE EFFICACY

Indication: Prevention of *C. difficile* Infection Recurrence

Guidelines

Guideline: Guidelines for diagnosis, treatment, and prevention of *C. difficile* infections

Reference: Surawicz CM, et al, 2013⁸

Comments: The only current means of prevention of *C. difficile* infection and antibiotic-associated diarrhea is the use of probiotics (eg, *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*). However, evidence for the use of probiotics in the prevention of *C. difficile* infection is insufficient, and recommendations for their use are not included in the guidelines. The guidelines do not recommend the use of intravenous immune globulin (IVIG), bile salt binders, or whole gut lavage for recurrent *C. difficile* infection. The recommended treatment for the first recurrence is the same treatment

regimen that was used for the initial episode; however, if the infection is severe, vancomycin is recommended. A second recurrence should be treated with a pulsed vancomycin regimen. In the case of a third recurrence following a pulsed vancomycin regimen, fecal microbiota transplant should be considered. Data on bezlotoxumab were not available at the time the guidelines were published.

Studies

Drug: Bezlotoxumab plus Actoxumab vs Bezlotoxumab vs Placebo (the actoxumab alone arm was discontinued after interim study analysis)

Reference: Wilcox M, et al, 2015^{2,17}

Study Design: Randomized, double-blind, multicenter study (combined results of MODIFY I and MODIFY II trials)

Study Funding: Merck

Patients: 2,655 adult patients with primary or recurrent *C. difficile* infection, including patients with multiple recurrences. Median patient age was 66 years; 57% of patients were women; and 2,580 (97%) patients received study medication. The full analysis set included 2,327 patients after discontinuation of the actoxumab arm; 53% of these patients were 65 years or older, 27% had prior *C. difficile* infection, 17% had severe *C. difficile* infection, and 11% were infected with 027 ribotype.

Intervention: Patients received standard-of-care antibiotics (metronidazole, vancomycin, or fidaxomicin) to treat *C. difficile* infection. The choice of antibiotic used to treat *C. difficile* infection was at the discretion of the investigator. In MODIFY I, patients received a single IV infusion of actoxumab 10 mg/kg plus bezlotoxumab 10 mg/kg, actoxumab 10 mg/kg alone, bezlotoxumab 10 mg/kg alone, or placebo. In MODIFY II, patients received a single IV infusion of actoxumab 10 mg/kg plus bezlotoxumab 10 mg/kg, bezlotoxumab 10 mg/kg alone, or placebo. The time of the bezlotoxumab infusion ranged from the day prior to the start of standard-of-care antibiotic therapy to 14 days after the start of antibiotic therapy (median, day 3).

Results

Primary Endpoint(s)

- Rate of *C. difficile* infection recurrence (new episode of diarrhea and positive stool test) was 15.4% with actoxumab plus bezlotoxumab, 16.5% with bezlotoxumab alone, and 26.6% with placebo (1-sided, $p < .001$); the

number needed to treat relative to placebo was 9 for actoxumab plus bezlotoxumab and 10 for bezlotoxumab alone.¹⁷ The recurrence rates were 17.4% in the bezlotoxumab group and 27.6% in the placebo group in MODIFY 1 and 15.7% and 25.7%, respectively, in MODIFY II.²

Secondary Endpoint(s)

- Recurrence rates in various subgroups (eg, 65 years or older, history of *C. difficile* infection, infected with 027 ribotype, severe *C. difficile* infection) were lower with active treatment versus placebo.
- Global cure rate (clinical cure of initial episode and no recurrent *C. difficile* infection) was 63.5% following bezlotoxumab alone (1-sided, $p < .001$ vs placebo), 58.1% with actoxumab plus bezlotoxumab (1-sided, $p = .043$), and 53.7% with placebo.¹⁷ Sustained clinical response was 60.1% in the bezlotoxumab group and 55.2% in the placebo group in MODIFY I (adjusted difference, 4.8%; 95% confidence interval [CI], -2.1% to 11.7%) and 66.8% and 52.1%, respectively, in MODIFY II (adjusted difference, 14.6%; 95% CI, 7.7% to 21.4%).²

Comments: The prescribing information only reports data from the bezlotoxumab plus standard-of-care versus placebo plus standard-of-care arms of this study. Pooled analysis of the 2 phase 3 studies (MODIFY I and MODIFY II) was conducted in 30 countries. The actoxumab-only arm in MODIFY I was discontinued by the safety board after the interim data analysis for efficacy and safety reasons. The results of this study indicate that the combination of actoxumab and bezlotoxumab provides no added benefit over bezlotoxumab alone.¹⁷ Using a computer-based Markov health state transition model from a third-party payer perspective, it was determined that bezlotoxumab plus standard of care has the potential to reduce the disease burden associated with *C. difficile* infection. This model used the recurrence rates from the pooled data from MODIFY I and MODIFY II along with transition probabilities and costs from the literature. The 3 parameters influencing cost effectiveness in the model were *C. difficile* infection-specific mortality, cost of a recurrent episode of *C. difficile* infection, and underlying recurrence rate.¹⁸

Post hoc analysis of the pooled data found a reduction in the total number of hospital days.¹⁹

In a similar study conducted using 2 neutralizing, fully human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1), the addition of these monoclonal antibodies to antibiotic agents reduced the recurrence of *C. difficile* infection compared to placebo plus antibiotic therapy. The mean duration of initial hospitalization did not differ between the 2 groups.²⁰

Post hoc analysis of the pooled data in patients receiving concomitant systemic antibiotics for other infections during treatment for *C. difficile* infection or during the 12-week follow-up period was also conducted. In those patients who received concomitant systemic antibiotics during treatment of the *C. difficile* infection, the recurrence rate for *C. difficile* was 17.3% in the bezlotoxumab group and 26.7% in the placebo group (treatment difference, -9.4%; 95% CI, -17.6% to -1%). Recurrence rate in patients using antibiotics during the post-standard-of-care follow-up period was 14.9% in the bezlotoxumab group and 21% in the placebo group (treatment difference, -6.1%; 95% CI, -14.4% to 1.9%).²¹

Limitations: Studies are published only as a meeting abstract. Patient population was limited to adults.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

None.²

Warnings and Precautions

Patients with a history of congestive heart failure may be at increased risk of heart failure or cardiovascular death after receiving bezlotoxumab therapy. In clinical trials, heart failure occurred at a higher incidence in bezlotoxumab-treated patients than with placebo (12.7% vs 4.8%) and occurred primarily in patients with underlying congestive heart failure.²

Treatment-emergent anti-bezlotoxumab antibodies have been reported.² The importance of this finding remains to be established.

There are no adequate and well-controlled studies of bezlotoxumab in pregnant women. Bezlotoxumab should be used during pregnancy only if clearly needed.²

Caution should be used when administering bezlotoxumab to a breast-feeding woman. No studies

have been conducted to assess the presence of bezlotoxumab in human milk or its effects on breast-feeding infants or milk production.²

Safety and efficacy of bezlotoxumab in patients younger than 18 years have not been established.²

ADVERSE REACTIONS

The most common adverse reactions reported in the 2 pivotal phase 3 trials in which bezlotoxumab was administered with an antibiotic (eg, metronidazole, vancomycin, fidaxomicin) were nausea, pyrexia, and headache.² Incidences of these adverse effects were similar between the bezlotoxumab plus standard-of-care antibiotic group and placebo plus standard-of-care antibiotic group: nausea occurred in 7% and 5%, pyrexia in 5% and 3%, and headache in 4% and 3% of patients, respectively.²

Infusion-related reactions (eg, nausea, fatigue, pyrexia, dizziness, headache, dyspnea, hypertension) occurred in 10% of the bezlotoxumab group and 8% of the placebo group. Most were mild to moderate in severity and resolved within 24 hours.²

DRUG INTERACTIONS

No metabolic drug-drug interactions with bezlotoxumab are expected because bezlotoxumab is eliminated by catabolism.²

Coadministration of other drugs simultaneously through the same infusion line is not recommended.²

RECOMMENDED MONITORING

Monitor for recurrence of *C. difficile* infection.

DOSING

Bezlotoxumab should be administered during antibacterial drug treatment for *C. difficile* infection. A single bezlotoxumab 10 mg/kg dose given as an IV infusion over 60 minutes is recommended.²

The safety and efficacy of repeat administration of bezlotoxumab have not been studied.²

Bezlotoxumab solution must be diluted with sodium chloride 0.9% injection or dextrose 5% injection prior to IV administration. It should be administered only as an IV infusion through a sterile, nonpyrogenic, low protein-binding 0.2 to 5 micron in-line or add-on filter into a central line or peripheral catheter; do not administer bezlotoxumab as an IV push or bolus.²

PRODUCT AVAILABILITY

The Biologics License Application for bezlotoxumab was submitted to the FDA in January 2016.²² Bezlotoxumab was approved in October 2016.¹

Bezlotoxumab is supplied in single-dose vials (1,000 mg per 40 mL [25 mg/mL]). The unopened vial should be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. The vials should not be frozen or shaken.²

The bezlotoxumab solution is preservative free. Once diluted, it should be stored either at room temperature for up to 16 hours or under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 24 hours. If refrigerated, allow the IV bag to come to room temperature prior to use. The 16- and 24-hour time recommendations include the time the solution is in storage through the duration of the infusion.²

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for bezlotoxumab.¹

CONCLUSION

Bezlotoxumab is not a substitute for antibiotic therapy in patients with *C. difficile* infection but is indicated for use in combination with standard-of-care antibiotics. The administration of the antibiotic and monoclonal antibody decreases the rate of *C. difficile* recurrence. The duration of protection against recurrent *C. difficile* infection with bezlotoxumab has not been established. Further studies are needed to determine which patients with *C. difficile* infection might benefit most from the addition of bezlotoxumab to antibiotic therapy for reduction in risk of recurrence.

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