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Subject: Bezlotoxumab (Zinplava) Injection

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DESCRIPTION:

Bezlotoxumab (Zinplava) is a human monoclonal antibody that binds to *Clostridium difficile* (*C. difficile*) toxin B thus inhibiting the binding of toxin B and neutralizing its effects. It does not bind toxin A. Actoxumab is the corresponding anti-toxin that binds toxin A. The toxins can damage the colonic epithelium leading to increased epithelial permeability, luminal fluid accumulation, and inflammation. Anti-toxin antibodies are naturally produced; however, the mechanisms controlling production are poorly understood. Lower endogenous, anti-toxin antibodies is thought to be a possible risk factor for recurrent disease. Bezlotoxumab was first FDA-approved in October 2016 to "reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence". It is the first therapy approved to reduce or prevent CDI recurrence. The prescribing information importantly notes that bezlotoxumab is NOT an antibacterial drug and should only be used in conjunction with antibacterial drug treatment of CDI.

The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) published guidelines on the management of CDI in 2017 and a focused update of the guidelines was released in 2021 (with new data for fidaxomicin and bezlotoxumab). *Clostridium difficile* infection is defined by the IDSA as: (1) the presence of diarrhea, defined as passage of three or more unformed stools in 24 or fewer consecutive hours; and (2) a stool test result positive for the presence of toxigenic *C. difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected. Based on the 2021 guideline update, initial episodes of CDI in adults should be treated with fidaxomicin 200 mg twice daily for 10 days (preferred) or oral vancomycin 125 mg four times daily for 10 days (alternative). The preferred use of fidaxomicin is a conditional recommendation based on moderate certainty of evidence. The recommendation places a high value in

the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative. Use of oral metronidazole 500 mg three times daily for 10 to 14 days should be reserved only for non-severe CDI when vancomycin or fidaxomicin are unavailable. Initial fulminant CDI (e.g., hypotension or shock, ileus, megacolon) should be treated with a combination of oral vancomycin 500 mg four times per day + IV metronidazole 500 mg three times per day (plus vancomycin retention enema if ileus is present). In all cases, therapy with the inciting antimicrobial agent(s) should be discontinued as soon as possible.

For the first recurrence of CDI, fidaxomicin is preferred (either 200 mg given twice daily for 10 days OR twice daily for 5 days followed by once every other day for 20 days). Vancomycin either in a tapered and pulsed regimen or as a standard course are acceptable alternatives. For patients with a recurrent CDI episode within the last 6 months, the guidelines suggest using bezlotoxumab as a co-intervention along with standard-of-care (SOC) antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence). In addition, in settings where logistics is not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. For treatment of the second or later recurrence of CDI, options include tapered and pulsed vancomycin regimen, fidaxomicin, vancomycin followed by rifaximin, or fecal microbiota transplantation.

There is mixed information and ongoing research on the independent risk factors that may best predict increased risk of CDI recurrence. The risk factors for increased risk of an initial CDI are better established. The most commonly accepted risk factors for CDI recurrence include advanced age, concurrent use of non-CDI antibiotics, and prior CDI recurrences. Other likely risk factors for recurrence include a hypervirulent *C. difficile* strain, patients with immunocompromising conditions or taking immunosuppressive medications, poor antibody-mediated immune response to toxin A or B, concurrent use of a proton pump inhibitors (PPI), and history of recent surgery. Other possible but less validated risk factors include but are not limited to severe CDI, diabetes, vancomycin-resistant enterococcus (VRE) colonization, renal insufficiency, advanced liver disease, extended time in hospital setting, and low serum albumin.

The FDA-approval of bezlotoxumab was based on two 12-week, randomized, double-blind, placebo-controlled, multicenter, Phase 3 trials (MODIFY-1 and 2) in patients receiving standard-of-care (SoC) antibacterial drugs for the treatment of CDI. Choice of SoC was at the discretion of the healthcare provider and included oral fidaxomicin (Dificid) (with or without IV metronidazole), oral metronidazole (Flagyl), or oral vancomycin (Vancocin) (with or without IV metronidazole). Enrolled patients were 18 years of age or older and had a confirmed diagnosis of CDI, which was defined as diarrhea (passage of 3 or more loose bowel movements in 24 or fewer hours) and a positive stool test for toxigenic *C. difficile* from a stool sample collected no more than 7 days before study entry. Patients were excluded if surgery for CDI was planned, or if they had uncontrolled chronic diarrhea. In MODIFY-1 patients were randomized 1:1:1:1 to receive a single IV infusion of actoxumab, bezlotoxumab, actoxumab + bezlotoxumab, or placebo. In MODIFY-2 there were three treatment arms, bezlotoxumab, actoxumab + bezlotoxumab, or placebo. The primary objective in both trials was to determine if treatment with a single infusion of the combination and the individual monoclonal antibodies decreases the proportion of subjects with CDI recurrence over a period of 12 weeks (day 85 ± 5 days) following clinical cure of the

initial episode (i.e., no diarrhea for 2 consecutive days following completion of standard-of-care treatment ≤14 days) as compared to placebo. CDI recurrence was defined as a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline episode. This primary endpoint was assessed in the Full Analysis Set (FAS), a subset of all randomized patients excluding those who did not receive study medication or did not have a positive stool test for toxigenic *C. difficile* at study entry or did not receive protocol defined SoC within a one-day window of bezlotoxumab for injection. The most important secondary endpoints were the proportion of subjects in each arm with an initial cure and a global cure (i.e. cure of the initial CDI episode and no recurrence through week 12). Of note, the FDA was primarily focused on the global cure outcome because the use of recurrence as the primary endpoint does not account for potential trial outcomes in which a drug causes a decrease in initial cures while providing protection against recurrence in those subjects who are initial cures.

A one-time dose of bezlotoxumab was associated with a higher rate of sustained clinical response (i.e., global cure) and a lower recurrence rate among patients achieving clinical cure of their presenting CDI. The baseline characteristics were similar across treatment arms. The median age was 65 years, 85% were white, 57% were female, and 68% were inpatients. A similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) and 4% of the patients received oral fidaxomicin as their SoC. Bezlotoxumab was given at any time during the treatment period, with a median day of administration of day 3. The following risk factors associated with a high risk of CDI recurrence or CDI-related adverse outcomes were present in the study population: 51% were ≥65 years of age, 39% received one or more systemic antibacterial drugs (during the 12-week follow-up period), 28% had one or more episodes of CDI within the six months prior to the episode under treatment (15% had two or more episodes prior to the episode under treatment), 21% were immunocompromised and 16% presented at study entry with clinically severe CDI (as defined by a Zar score of ≥2). A hypervirulent strain (ribotypes 027, 078 or 244) was isolated in 22% of patients who had a positive baseline culture, of which 87% (189 of 217 strains) were ribotype 027. Table 1 below shows the results for both trials.

Table 1: Outcomes of MODIFY-1 and 2 Trials

	MODIFY-1			MODIFY-2		
Outcome	**Bezlotoxumab (n=386)**	**Placebo (n=395)**	**Difference (95% CI, p-value)**	**Bezlotoxumab (n=395)**	**Placebo (n=378)**	**Difference (95% CI, p-value)**
Sustained clinical response among those achieving clinical cure of presenting episode (global cure)	60.1%	55.2%	4.8% (-2.1, 11.7, p=0.1647)	66.8%	52.1%	14.6% (7.8, 21.4, p<0.0001)
Recurrence rate among those achieving clinical cure of presenting episode	17.4%	27.6%	-10.1% (-15.9, -4.3, p=0.0006)	15.7%	25.7%	-9.9% (-15.5, -4.2)
Clinical cure of presenting episode	77.5%	82.8%	-5.3% (-10.9, 0.3, p=0.0622)	82.5%	77.8%	4.8% (-0.9, 10.4, p=0.0973)

In MODIFY-1, the initial clinical cure rate of the presenting CDI episode was lower in the bezlotoxumab arm as compared to the placebo arm; however, in MODIFY-2, the clinical cure rate was lower in the

placebo arm. Subjects in the bezlotoxumab and placebo arms who did not achieve clinical cure of the presenting CDI episode received a mean of 18 to 19 days of SoC and had a mean of 4 additional days of diarrhea following completion of SoC. Additional analyses showed that by 3 weeks post study drug infusion the clinical cure rates of the presenting CDI episode were similar between treatment arms.

POSITION STATEMENT:

Initiation of bezlotoxumab (Zinplava) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. The member has a confirmed diagnosis of *Clostridium difficile* infection (CDI) as evidenced by **BOTH** of the following ("a" and "b"):
    a. Passage of 3 or more loose bowel movements in 24 or fewer hours
    b. A positive stool test for toxigenic *C. difficile* – Medical record or laboratory documentation of the positive test result must be submitted. Any of the following test methodologies are acceptable:
        i. Nucleic acid amplification test [such as polymerase chain reaction (PCR)]
        ii. Toxin A and B enzyme immunoassay (EIA) test
        iii. Cell culture cytotoxicity neutralization assay (CCNA)
        iv. Toxigenic stool culture
2. The member is starting or is currently receiving appropriate antibiotic treatment for CDI which includes any of the following antibiotics:
    a. Oral vancomycin (Vancocin) (with or without IV metronidazole) for at least 10 days
    b. Oral vancomycin for at least 10 days followed by rifaximin (Xifaxan) for 20 days
    c. Oral fidaxomicin (Dificid) (with or without IV metronidazole) for at least 10 days
3. Bezlotoxumab will be administered during antibacterial drug treatment for member's CDI
4. The member is at high-risk for CDI recurrence as evidenced by **ONE** or more of the following risk factors ("a", "b", "c". "d", or "e"):
    a. Member has had one or more previous CDIs requiring treatment in the past 6 months
    b. Member is 65 years of age or older
    c. Member is immunocompromised defined as **ANY** of the following:
        i. Active hematological malignancy
        ii. Current use of an antineoplastic or immunomodulating agent
        iii. Current use of chronic corticosteroids
        iv. Asplenia
        v. Current neutropenia or pancytopenia
        vi. Prior solid organ transplant
        vii. Having AIDS or other immunodeficient condition

d. Continuation of systemic antibiotic(s) for a non-*Clostridium difficile* infection is clinically necessary during CDI treatment (valid rationale must be provided)

e. Member's CDI is caused by a confirmed hypervirulent strain of *C. difficile* defined as ribotypes 027,078, or 244

5. The member is 18 years of age or older
6. The dosage does not exceed 10 mg/kg to be given as a single intervenous (IV) dose
7. The member has not received a previous dose of bezlotoxumab in the past 6 months

Approval duration: One dose within 4 weeks of approval date

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated to reduce recurrence of Clostridium difficile infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.
- Limitation of Use: bezlotoxumab is **NOT** indicated for the treatment of CDI. Bezlotoxumab is not an antibacterial drug and should only be used in conjunction with antibacterial drug treatment of CDI.
- The recommended is dose is a single dose of 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes during antibacterial treatment for Clostridium difficile infection (CDI). The efficacy and safety of repeat administration have not been studied.
- Bezlotoxumab must be diluted with 0.9% sodium chloride injection or 5% dextrose injection to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 10 mg/mL. Administer the diluted solution as an intravenous infusion over 60 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

Dose Adjustments

- No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with hepatic impairment and patients with normal hepatic functio; it appears that no dosage adjustments are needed.
- No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with renal impairment and patients with normal renal function; it appears that no dosage adjustments are needed.

Drug Availability

- 1,000 mg/40 mL (25 mg/mL) single-dose, preservative-free vial
- Store in a refrigerator, 2ºC to 8ºC (36ºF to 46ºF) in original carton to protect from light. Do not freeze or shake.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Heart Failure**: Was reported more commonly in bezlotoxumab-treated patients with a history of congestive heart failure (CHF) in the two Phase 3 clinical trials. In patients with a history of CHF, 12.7% (15/118) of bezlotoxumab -treated patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure during the 12-week study period. Additionally, inpatients with a history of CHF, there were more deaths in bezlotoxumab -treated patients, 19.5% (23/118) than in placebo-treated patients, 12.5% (13/104) during the 12-week study period. In patients with a history of CHF, bezlotoxumab should be reserved for use when the benefit outweighs the risk.
- **Adverse Reactions**: The most common adverse reactions following treatment with bezlotoxumab (reported in ≥4% of patients within the first 4 weeks of infusion and with a frequency greater than placebo) were nausea (7% vs. 5%), pyrexia (5% vs. 3%), and headache (4% vs. 3%).
- **Immunogenicity**: Following treatment with bezlotoxumab in both phase 3 trials, none of the 710 evaluable patients tested positive for treatment-emergent anti-bezlotoxumab antibodies.
- **Drug Interactions**: Since bezlotoxumab is eliminated by catabolism, no metabolic drug-drug interactions are expected.
- **Pregnancy and Lactation**: Adequate and well controlled studies with bezlotoxumab have not been conducted in pregnant women. No animal reproductive and developmental studies have been conducted with bezlotoxumab. There is no information regarding the presence of bezlotoxumab in human milk, the effects on the breast-fed infant, or the effects on milk production.
- **Pediatric Use**: The safety and efficacy of bezlotoxumab in patients below 18 years of age have not been established.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0565	Injection, bezlotoxumab, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/09/22.

GUIDELINE UPDATE INFORMATION:

03/15/17	New Medical Coverage Guideline.
07/01/17	Addition of HCPCS code C9490.
01/01/18	Annual HCPCS coding update: added HCPCS code J0565 and removed code C9490
01/15/18	Review and revision to guideline consisting of updating the position statement and references.
06/15/18	Updated ICD-10 coding information.
01/15/19	Review and revision to guideline consisting of updating the description, position statement and references.
04/15/22	Revision to guideline consisting of updating the description, position statement and references.