

Corporate Medical Policy

Zinplava (bezlotoxumab)

File Name:	zinplava_(bezlotoxumab)
Origination:	6/2017
Last CAP Review:	5/2020
Next CAP Review:	5/2021
Last Review:	5/2020

Description of Procedure or Service

Clostridium difficile (*C. difficile*) is a gram-positive anaerobic bacteria that forms spores and produces toxins, including toxin B, causing antibiotic-associated colitis. *Clostridium difficile* infection (CDI) occurs when this bacteria colonizes the human intestinal tract following disruption of the normal gut flora (often associated with antibiotic therapy). The toxins released by *C. difficile* bind to receptors on intestinal epithelial cells, which leads to mucosal damage and inflammation. Symptoms of CDI range from mild-to-severe diarrhea, abdominal pain and fever, to more serious intestinal conditions such as fulminant colitis.

CDI recurrence is the development of a new episode of diarrhea associated with a positive stool test for *C. difficile* toxin following clinical cure of the initial CDI episode.

According to the Centers for Disease Control and Prevention (CDC), *C. difficile* infected nearly 500,000 individuals in 2011. 83,000 of those that contracted the infection experienced at least one recurrence, and approximately 29,000 deaths were reported within 30 days of the initial diagnosis. The infection is preventable using infection control recommendations and appropriate use of antibiotics (CDC, 2015).

Bezlotoxumab (Zinplava™) is a human monoclonal antibody that binds to *C. difficile* toxin B, thus inhibiting the binding of toxin B and neutralizing its effects. 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 are thought to be a possible risk factor for recurrent disease. Zinplava is not an antibacterial drug and should only be used in conjunction with antibacterial drug treatment of CDI.

On October 21, 2016 intravenously administered bezlotoxumab was the first human monoclonal antibody (mAb) to achieve accelerated approval and breakthrough therapy status by the U.S. Food and Drug Administration (FDA), as it is the first therapeutic option indicated to reduce recurrence of CDI in individuals 18 years of age or older who are receiving standard-of-care (SOC) antibiotics for CDI and are at a high risk for CDI recurrence.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Zinplava (bezlotoxumab) when the medical necessity criteria and guidelines shown below are met.

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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Zinplava (bezlotoxumab) is covered

A single injection of bezlotoxumab is considered medically necessary to reduce recurrence of Clostridium difficile infection in individuals 18 years of age or older when all the following criteria are met:

- A. Confirmed Clostridium difficile infection when both of the criteria below are met:
1. Passage of three or more loose stools within 24 hours or less; **and**
 2. Positive stool test for toxigenic Clostridium difficile from a stool sample collected not more than 7 days prior to scheduled infusion; **and**
- B. Currently receiving antibacterial therapy for Clostridium difficile infection; **and**
- C. Individual is at high risk of Clostridium difficile infection recurrence meeting any one of the following:
1. Individual 65 years of age or older, with a history of Clostridium difficile infection in the past 6 months; **or**
 2. Immunocompromised state; **or**
 3. Severe Clostridium difficile infection at presentation; **or**
 4. Clostridium difficile ribotype 027

When Zinplava (bezlotoxumab) is not covered

The use of bezlotoxumab is considered **investigational** when the above criteria are not met, and for all other conditions, including but not limited to first-line therapy.

Zinplava should be used only in conjunction with antibacterial drug treatment of CDI.

Policy Guidelines

Clinically severe C. difficile infection (CDI) is defined by one of the following:

The College of Gastroenterology (ACG, 2013):

- Albumin <3g/dl plus one of the following;
- White blood cell (WBC) > or equal to 15,000 cells/mm³; or
- Abdominal tenderness

The Infectious Disease Society of America (IDSA):

- WBC > or equal to 15,000 cells/mm³ and serum creatinine level >1.5x baseline creatinine level

ZAR (2007) score ≥ 2:

- Age >60 years old (1 point)
- Body temperature >38.3°C (>100°F) (1 point);
- Albumin level 2.5mg/dL (1 point);
- Peripheral white blood cell count >15,000 cells/mm³ within 48 hours (1 point);
- Endoscopic evidence of pseudomembranous colitis (2 points); and

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- Treatment in Intensive Care Unite (2 points)

The FDA approval of bezlotoxumab was based on safety and efficacy demonstrated in two Phase III randomized, multicenter, double-blind, placebo-controlled trials. Notable enrollment criteria for both trials included individuals with confirmed diagnosis of CDI (≥ 3 loose stools in ≤ 24 hours and + stool test for toxigenic *C. difficile* collected within the previous 7 days) who were 18 years of age or older and receiving or planning to receive SOC therapy for CDI (antibiotics). Subjects recorded stools in a daily log and study personnel determined if a recurrence had occurred. The primary outcome in both studies was the proportion of participants who had a CDI recurrence in the treatment arms compared to the placebo. A notable secondary outcome was global cure rate.

The first Phase III study, P001, was an adaptive, factorial trial which enrolled participants into one of the following four study arms: actoxumab (anti-toxin A antibody), bezlotoxumab (anti-toxin B antibody), actoxumab + bezlotoxumab, or placebo (0.9% sodium chloride). Study treatment was for the prevention of CDI recurrence in subjects who were receiving antibacterial treatment for CDI. Enrollment in the actoxumab-only arm was halted early due to an interim analysis based on safety concerns relative to the placebo arm and inferior efficacy relative to the actoxumab + bezlotoxumab arm. The remaining three arms continued enrollment through trial end. In total, 1452 individuals were randomized into the trial. In the actoxumab + bezlotoxumab and bezlotoxumab only arms, a significantly lower proportion of individuals had a CDI recurrence; 15.9% ($p < 0.0001$) and 17.4% ($p = 0.0006$), respectively, as compared to 27.6% in the placebo arm. The difference between the proportion in the actoxumab + bezlotoxumab and bezlotoxumab only arms was not statistically different ($p = 0.594$). The difference in the secondary endpoint of global cure did not reach statistical significance in the actoxumab + bezlotoxumab arm (58.7%) or bezlotoxumab (60.1%) in comparison to placebo (55.2%).

In the second Phase III study, P002, 1203 participants were randomized similarly to Study P001 into one of four study arms, although the actoxumab arm alone was not included. There was a significantly lower proportion of subjects with CDI recurrence in the actoxumab + bezlotoxumab (14.9%; $p = 0.0002$) and bezlotoxumab (15.7%; $p = 0.0006$) arms as compared to the placebo arm (25.7%); there was no significant difference between the actoxumab + bezlotoxumab and bezlotoxumab only arms ($p = 0.748$). The proportion of study participants who achieved a global cure was significantly higher in the bezlotoxumab arm compared to the placebo ($p < 0.001$), but not in the actoxumab + bezlotoxumab arm compared to placebo ($p = 0.137$).

Overall, the combination of actoxumab + bezlotoxumab was not found to enhance efficacy in the prevention of recurrence of CDI over bezlotoxumab alone. Bezlotoxumab, given as a single IV infusion, had an overall favorable safety profile with rates of adverse events and deaths similar to placebo. There was no increase in adverse events related to potential immune-mediated reactions in the bezlotoxumab arm compared to the placebo arm. Numerically, there was a higher number of serious adverse events and deaths in the bezlotoxumab arm compared to the placebo arm amongst subjects who reportedly had congestive heart failure at baseline.

The recommended dose of Zinplava (bezlotoxumab) is a single dose of 10mg/kg administered as an intravenous infusion, diluted in either 0.9% Sodium Chloride or 5% Dextrose injection, over 60 minutes. Zinplava is to be given by a healthcare professional.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

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Applicable codes: J0565

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

U.S. Food and Drug Administration (FDA). FDA approves Zinplava (bezlotoxumab) to decrease risk of Clostridium difficile infection (CDI). FDA News. Rockville, MD: FDA; October 21, 2016. Available at: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm528793.htm> (Accessed May 23, 2017)

U.S. Food and Drug Administration (FDA). Zinplava (bezlotoxumab) Package Insert. Whitehouse Station, NJ. Merck Sharp & Dohme Corp. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761046s000lbl.pdf (Accessed May 22, 2017)

Yang Z, Ramsey J, Hamza T, et al. Mechanisms of protection against clostridium difficile infection by the monoclonal antitoxin antibodies Actoxumab and Bezlotoxumab. Infect Immun. 2015; 83(2):822-831.

Christina M, Surawicz MD, Lawrence J, et al. Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. Am J Gastroenterol. 2013; 108:478-498.

Zar FA, Bakkanagari SR et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis, 2007; 45(3):302-307.

Centers for Disease Control and Prevention. Healthcare-associated infections (HAIs). Updated September 23, 2015. Available at: https://www.cdc.gov/HAI/organisms/cdiff/Cdiff_clinicians.html Accessed on May 23, 2017

Medical Director review 6/2017

Specialty Matched Consultant Advisory Panel review 5/2018

Specialty Matched Consultant Advisory Panel review 5/2019

Specialty Matched Consultant Advisory Panel review 5/2020

Policy Implementation/Update Information

- 6/30/17 Original policy developed titled, “Zinplava (bezlotoxumab)” with policy statement, “BCBSNC will provide coverage for Zinplava (bezlotoxumab) when the medical necessity criteria and guidelines shown below are met.” Medical Director review 6/2017. Policy noticed 6/30/17 for effective date 9/29/17. Code C9490 and J3590 will be noticed 7/1/17, effective for PPA 10/1/17. (jd)
- 12/29/17 Code section updated. Code J0565 added to policy, replacing C9490. Code is effective 1/1/18. (jd)
- 1/26/18 Code C9490 added to policy. (jd)
- 6/8/18 Updated “Description of Procedure or Service” section to provide clarity. Updated Billing/Coding section to remove codes C9490 and J3590 termed 12/31/17 with code J0565 effective 1/1/18. Reference added. Specialty Matched Consultant Advisory Panel review 5/23/2018. No change to policy intent. (krc)

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5/28/19 Specialty Matched Consultant Advisory Panel review 5/15/2019. No change to policy intent. (krc)

6/23/20 Specialty Matched Consultant Advisory Panel review 5/20/2020. No change to policy intent. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.