Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Bezlotoxumab (Zinplava®)	MP-RX-FP-109-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ DRUG TYPE B

Service Description

This document addresses the use of Bezlotoxumab (Zinplava®), a monoclonal antibody, approved by the Food and Drug Administration (FDA) to reduce the recurrence of Clostridiodes difficile infection (CDI).

Background Information

Bezlotoxumab (Zinplava) is a fully human monoclonal IgG1/kappa antibody that binds to Clostridiodes (formerly Clostridium) difficile toxin B. Zinplava is approved by the Food and Drug Administration to reduce recurrence of Clostridiodes difficile infection (CDI) in individuals one year of age or older who are receiving antibacterial therapy for CDI and are at high risk for CDI recurrence. Zinplava is not an antibiotic and should only be used in combination with antibacterial therapy targeted for CDI (including Dificid, oral vancomycin and metronidazole).

The FDA approval of Zinplava was based on two Phase III randomized, 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 a positive 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 standard of care antibiotic therapy for CDI. The primary outcome in both studies was the proportion of participants who had a CDI recurrence. A notable secondary outcome was global cure rate.

The two trials together enrolled more than 2600 participants into one of four study arms: actoxumab (anti-toxin A antibody), Zinplava (anti-toxin B antibody), actoxumab + Zinplava or placebo. Enrollment in the actoxumab arm was halted during the first trial due to safety concerns relative to placebo and low efficacy compared to the combination arm. In the first trial, there was a significantly lower proportion of individuals with CDI recurrence in the actoxumab + Zinplava (15.9%; $p<0.0001$) and Zinplava only (17.4%; $p=0.0006$) arms as compared to the placebo arm (27.6%). There was no significant difference between the actoxumab + Zinplava and Zinplava only arms. There was also no significant difference in the secondary endpoint of global cure.

In the second trial, there was a significantly lower proportion of individuals with CDI recurrence in the actoxumab + Zinplava (14.9%; $p=0.0002$) and Zinplava only (15.7%; $p=0.0006$) arms as compared to the placebo arm (25.7%). There was no significant difference between the actoxumab + Zinplava and Zinplava only arms. The proportion of participants who achieved a global cure was significantly higher in the Zinplava arm compared to the placebo arm ($p<0.001$) but not in the actoxumab + Zinplava arm compared to placebo.

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The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) published a 2021 focused update to the 2017 CDI management guidelines. Recommendations for the treatment of an initial episode of CDI in adults include Dificid as the preferred option with oral vancomycin as an alternative. Recommendations for CDI recurrence include Dificid in a standard or extended-pulse regimen as the preferred option with standard or tapered/pulsed vancomycin as an alternative. For individuals with a recurrent CDI episode within the last 6 months, IDSA/SHEA recommends using Zinplava with standard of care antibiotics. Individuals with a primary CDI episode and other risk factors for CDI recurrence (including age ≥65 years, immunocompromised state and severe CDI) may also benefit from the addition of Zinplava.

Definitions and Measures

- Severe Clostridiodes difficile infection can be defined by one of the following:
  - Infectious Disease Society of America (IDSA) IDSA, 2017):
    - white blood cell ≥15,000 cells/mL; **OR**
    - serum creatinine level >1.5 mg/dL
  - ZAR score ≥ 2 (Zar, 2007)
    - age >60 years old = 1 point
    - body temperature >38.3°C (>100.9°F) = 1 point
    - albumin level <2.5 mg/dL = 1 point
    - peripheral white blood cell >15,000 cells/mm3 within 48 hours = 1 point
    - endoscopic evidence of pseudomembranous colitis = 2 points
    - treatment in Intensive Care Unit (ICU) = 2 points

Approved Indications

A. To reduce recurrence of Clostridiodes difficile infection (CDI) in individuals 1 year of age and older who are receiving antibacterial therapy for CDI and are at high risk for CDI recurrence.

Other Uses

i. N/A

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J0565	Injection, bezlotoxumab, 10 mg [ZINPLAVA]

ICD-10	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Clinical Criteria

Bezlotoxumab (Zinplava®)

A. Criteria for Initial Approval

Requests for Zinplava (bezlotoxumab) may be approved if the following criteria are met:

i. Individual has *Clostridiodes difficile* infection confirmed by:
   A. Passage of three or more loose stools within 24 hours or less; **AND**
   B. Positive stool test for toxigenic *Clostridiodes difficile* from a stool sample collected no more than 7 days prior to scheduled infusion; **AND**

ii. Individual is currently receiving antibacterial therapy for Clostridiodes difficile infection (including Dificid, metronidazole, or oral vancomycin); **AND**

iii. Individual is at high risk of *Clostridiodes difficile* infection recurrence based on one of the following:
   A. 65 years of age or older; **OR**
   B. History of *Clostridiodes difficile* infection in the past 6 months; **OR**
   C. Immunocompromised state; **OR**
   D. Severe *Clostridiodes difficile* infection at presentation*; **OR**
   E. *Clostridiodes difficile* ribotype 027.

B. Criteria for Continuation of Therapy

i. Zinplava is administered as a single dose infusion. Repeated administration have not been studied.

C. Conditions not Covered

i. Zinplava (bezlotoxumab) may not be approved for the following:
   A. First-line treatment for Clostridiodes difficile infection; **OR**
   B. Use in combination with Rebyota or Vowst during the same Clostridiodes difficile infection episode; **OR**
   C. May not be approved when the above criteria are not met and for all other indications.

D. Authorization Duration

i. Approval Duration: one injection

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Zinplava 1,000mg/40ml (25mg/ml) single dose vial	10 mg/kg IV (single dose)
Exceptions	
Zinplava should only be used in conjunction with antibacterial drug treatment of CDI.	

Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: September 10, 2022.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021;73(5):1029-1044.
4. Kelly CP, Lamont JT, Bakken JS. Clostridiodes difficile infection in adults: Treatment and prevention. Updated: August 3, 2021. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: September 10, 2022.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
6. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):987-994.
7. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for the prevention of recurrent Clostridium difficile infection. N Eng J Med. 2017; 376(4):305-317.
8. Zar FA, Bakkanagari SR, at 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.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 9/2/2025	Minimal changes; Word formatting. Coding reviewed: No changes.	9/5/2025	9/16/2025
Annual Review. 9/27/2024	Added sections: criteria for continuation of therapy, limits or restrictions (St wording and recommended dosage). Add may not approve criteria for combination use with Rebyota or Vowst. Wording and formatting changes. Coding Reviewed: Removed ICD10-PCS XQ033A3, XW043A3.	3/14/2025	4/2/2025
Policy Inception 9/27/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023