Medical Drug Clinical Criteria

Subject:	Zinplava (bezlotoxumab)		
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Table of Contents

Overview

This document addresses the use of Zinplava (bezlotoxumab), 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 following risk factors associated with a high risk of CDI recurrence 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, 21% were immunocompromised, 16% presented with clinically severe CDI and 22% had a hypervirulent strain (ribotypes 027, 078 or 244) of Clostridiodes difficile (87% were ribotype 027).

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.

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.

Clinical Criteria

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.

Zinplava (bezlotoxumab)

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

I. Individual has -*Clostridiodes difficile* infection ~~confirmed~~ demonstrated 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.

Zinplava (bezlotoxumab) may not be approved for the following:

I. First-line treatment for *Clostridiodes difficile* infection; **OR**

II. Use in combination with Rebyota or Vowst during the same Clostridiodes difficile infection episode; **OR**

~~II.~~ III. May not be approved when the above criteria are not met and for all other indications.

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Approval Duration: one injection

***Note:** 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/mm^3 within 48 hours = 1 point • endoscopic evidence of pseudomembranous colitis = 2 points • treatment in Intensive Care Unit (ICU) = 2 points

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0565	Injection, bezlotoxumab, 10 mg [ZINPLAVA]

CPT

96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug4
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour4

ICD-10 Diagnosis

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

Document History

Revised: 9/11/2023
Document History:
- 9/11/2023 – Annual Review: Add may not approve criteria for combination use with Rebyota or Vowst. Wording and formatting changes. Coding Reviewed: Removed ICD10-PCS XQ033A3, XW043A3. Added CPT 96413, 96365.

- 9/12/2022 – Annual Review: Clarified antibiotic therapy for *Clostridiodes difficile* infection. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM A04.71, A04.72. Removed ICD-10-CM A04.71-A04.72.
- 9/13/2021 – Annual Review: Remove ACG definition of severe CDI as the updated guideline definition aligns with the IDSA definition. Coding reviewed: No changes.
- 9/14/2020 – Annual Review: No changes. Coding Review: No changes.
- 09/9/2019 – Annual Review: Wording and formatting changes. Coding reviewed. No changes.
- 11/16/2018 – Annual Review: Initial P&T review of ING-CC-0046 Zinplava (bezlotoxumab). Remove age criteria as no pediatric safety concern. In CDI recurrence criteria, separate age and history of CDI into separate risk factors to align with high risk subgroups included in clinical trial. Wording updates for clarity. Update definition of severe CDI to reflect updated IDSA treatment guidelines. HCPCS and ICD-10 coding review: No changes.

References

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, 2023.
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: May 11, 2023. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: September 10, 2023.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. 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.