

Clinical Policy: Bezlotoxumab (Zinplava)

Reference Number: CP.PHAR.300

Effective Date: 02.01.17

Last Review Date: 02.25

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Bezlotoxumab (Zinplava[™]) is a human monoclonal antibody that binds to *Clostridium difficile* toxin B.

FDA Approved Indication(s)

Zinplava is indicated to reduce recurrence of *Clostridioides difficile* infection (CDI) in adults and pediatric patients 1 year of age and older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

Limitation(s) of use: Zinplava is not indicated for the treatment of CDI. Zinplava is not an antibacterial drug. Zinplava should only be used in conjunction with antibacterial drug treatment of CDI.

Policy/Criteria

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

It is the policy of health plans affiliated with Centene Corporation[®] that Zinplava is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria**A. *Clostridium difficile* Infection** (must meet all):

1. Diagnosis of CDI confirmed by documentation of positive *Clostridium difficile* test;
2. Age $\geq$ 1 year;
3. Member will receive or is currently receiving concomitant antibacterial drug treatment for CDI (e.g., vancomycin, fidaxomicin);
4. Member has had at least one episode of CDI recurrence (total 2 episodes) in the previous 6 months and has been treated with appropriate treatment for CDI (e.g., vancomycin, fidaxomicin), including a pulsed vancomycin regimen;
**Treatment failure for CDI may be declared in as little as 48 hours in patients with severe disease who fail to improve.*
5. Dose does not exceed 10 mg/kg once.

Approval duration: 3 months (1 dose only)

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

- a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. *Clostridium difficile* Infection

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CDI: *Clostridium difficile* infection

FDA: Food and Drug Administration
 IDSA: Infectious Diseases Society of America

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Dificid [®] (fidaxomicin)	200 mg PO BID for 10 days; for recurrences, may use alternative regimen of 200 mg PO BID for 5 days, followed by QOD for 20 days	See regimen
vancomycin	Adult: 125 mg PO QID for 10 days; for recurrences, may use a tapered and pulsed regimen Pediatric: 10 mg/kg/dose PO QID	See regimen

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- The new term *Clostridioides difficile* was introduced in 2019. It may be used interchangeably with *Clostridium difficile*.
- Zinplava is the only medication approved to reduce the recurrence of CDI.
- Zinplava was studied in two randomized placebo controlled trials in which patients received a single IV infusion of Zinplava. The efficacy of repeat courses of Zinplava therapy has not been established.
- Approximately 35% of CDI patients experience recurrence after the initial treatment and resolution of diarrhea. Of those who have a primary recurrence, 40% will have another CDI episode, and after 2 recurrences, the chance of an additional episode increases to as high as 65%.
- Per the IDSA Clinical Practice Guidelines for *Clostridium difficile* Infection 2017 Update:
 - An incident case is one with a new primary symptom onset (i.e., in the previous 8 weeks, there was not an episode of positive symptoms with positive *C. diff* result) and positive *C. diff* assay result.
 - A recurrent infection is an episode of symptom onset with a positive assay result following an episode with positive assay result in the previous 2–8 weeks.
- Per the IDSA 2021 Focused Update for *Clostridium difficile* Infection in adults:
 - Fidaxomicin (standard or extended-pulsed regimen) is the preferred first-line treatment for patients with recurrent CDI episode(s).

- Vancomycin in a tapered and pulsed regimen or as a standard course are acceptable alternatives for first CDI recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.
- Examples of treatment regimens for recurrence:
 - Adult: Vancomycin 125 mg PO QID for 10 days (may be followed by rifaximin 400 mg PO TID for 20 days)
 - Pediatric: Vancomycin 10 mg/kg PO QID for 10 days (may be followed by rifaximin* for 20 days)
** rifaximin is not FDA-approved for use in children <12 years of age*
 - Tapered and pulsed regimens of vancomycin (e.g., vancomycin PO 125 mg QID for 10 to 14 days, then BID for 1 week, then QD for 1 week, then every 2 or 3 days for 2 to 8 weeks)
 - Adult: Fidaxomicin 200 mg PO BID for 10 days
 - Adult: Fidaxomicin 200 mg PO BID for 5 days followed by once every other day for 20 days
 - Fecal microbiota transplantation

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CDI recurrence	10 mg/kg as a single dose IV infusion over 60 minutes	10 mg/kg

VI. Product Availability

Single-dose vial for injection: 1,000 mg/40 mL (25 mg/mL)

VII. References

1. Zinplava Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc; May 2023. Available at: https://www.merck.com/product/usa/pi_circulars/z/zinplava/zinplava_pi.pdf. Accessed October 22, 2024.
2. Antimicrobial Drugs Advisory Committee. Bezlotoxumab injection briefing document (BLA 761046). Published June 9, 2016. Available at <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm505291.pdf>. Accessed October 31, 2024.
3. Surawicz CM, Brandt LJ, Binion DG et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013 Apr;108(4):478-98; quiz 499. doi: 10.1038/ajg.2013.4. Epub 2013 Feb 26.
4. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45(3):302-7.
5. Lessa FC, Mu Y, Bamber WM et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825-34. doi: 10.1056/NEJMoa1408913
6. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 updated by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. March 2018;66(7):987-994.

7. Johnson S, Laverigne V, Skinner AM, et al. Clinical Practice Guideline 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. CID 2021; 73 (1 September): e1029-1044.
8. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. Am J Gastroenterol 2021;116:1124 - 1147.
9. Clinical Pharmacology [database online]. Tampa, FL: Elsevier; 2023. URL: www.clinicalkey.com/pharmacology.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0565	Injection, bezlotoxumab, 10 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: revised I.A.4 to allow use of Zinplava after the first recurrence rather than the second based on clinical concerns with delaying therapy, claims data review, and market analysis; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.20.20	02.21
1Q 2022 annual review: no significant changes; updated Appendix D per 2021 IDSA guideline update; references reviewed and updated.	09.29.21	02.22
Template changes applied to other diagnoses/indications.	09.21.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	10.12.22	02.23
Removed metronidazole as an example of prior antibiotic therapy; added therapeutics alternatives in Appendix B.	05.23.23	08.23
1Q 2024 annual review: updated CDI age requirement from ≥ 18 years to ≥ 1 year per FDA pediatric expansion; references reviewed and updated.	11.16.23	02.24
1Q 2025 annual review: no significant changes; references reviewed and updated.	10.22.24	02.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional

organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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