Clinical Policy: Bezlotoxumab (Zinplava)

Reference Number: ERX.SPA.03
Effective Date: 04.01.17
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

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 the 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(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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 ≥ 18 years;
3. Member will receive or is currently receiving concomitant antibacterial drug treatment for CDI (e.g., metronidazole, 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 an appropriate treatment for CDI (e.g., metronidazole, 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

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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
Not applicable

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 chances 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:
    - Vancomycin 125 mg PO QID for 10 days (may be followed by rifaximin 400 mg PO TID for 20 days)
    - 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)
    - Fidaxomicin 200 mg PO BID for 10 days
    - 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
Reduce recurrence of CDI	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; October 2016. Available at: https://www.merck.com/product/usa/pi_circulars/z/zinplava/zinplava_pi.pdf. Accessed September 29, 2021.
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 September 29, 2021.
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, Lavergne 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Added age requirement in accordance with prescribing information; References reviewed and updated.	11.03.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.06.19	02.20
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 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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.