bezlotoxumab (Zinplava™)

Policy # 00560
Original Effective Date: 05/17/2017
Current Effective Date: 08/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider bezlotoxumab (Zinplava™)‡ to reduce the recurrence of *Clostridium difficile* infection to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for bezlotoxumab (Zinplava) will be considered when the following criteria are met:

- Patient currently has a diagnosis of *Clostridium difficile* infection (as confirmed by appropriate testing; AND
- Patient is 1 year of age or older; AND
- Patient has NOT previously received Zinplava for the current *Clostridium difficile* infection; AND
- Zinplava is dosed at 10 mg/kg as a one-time dose; AND
- Patient will receive standard of care antibiotics for the treatment of *Clostridium difficile* infection in conjunction with Zinplava; AND
- Patient is at high risk for *Clostridium difficile* infection recurrence, which is evidenced by a prior history of *Clostridium difficile* infection within the past 6 months AND at least ONE of the following:
    - Patient is 65 years of age or older; OR
    - Patient has severe *Clostridium difficile* infection, as evidenced by a ZAR score of greater than or equal to 2, WBC ≥ 15,000 cells/mL, OR serum creatinine level > 1.5 mg/dL; OR

  - Patient is immunocompromised (e.g. active hematological malignancy, current use of an antineoplastic or immunomodulating agent, current use of chronic corticosteroids, asplenia, current neutropenia or pancytopenia, prior solid organ transplant, having AIDS or other immunodeficient condition); AND.
- The patient will not use in combination with fecal microbiota products [i.e., fecal microbiota spores, live-brpk (Vowst™)‡ and fecal microbiota, live-jslm (Rebyota™)‡] during the same *Clostridium difficile* infection episode.

Note: The ZAR score is calculated as follows:

- *Age >60 (1 point)*
- *Body temperature >100 degrees Fahrenheit (1 point)*
- *Albumin level <2.5 mg/dL (1 point)*
- *Peripheral WBC >15,000 cells/mm3 within 48 hours (1 point)*
- *Endoscopic evidence of pseudomembranous colitis (2 points)*
- *Treatment in ICU (2 points)*

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of bezlotoxumab (Zinplava) when the patient selection criteria are not met to be **investigational.***

Background/Overview

Zinplava is a human monoclonal antibody that binds to *Clostridium difficile* toxin B and is indicated to reduce the recurrence of *Clostridium difficile* infection in patients 1 year of age and older who are receiving antibacterial drug treatment of *Clostridium difficile* infection (CDI) and are at high risk for *Clostridium difficile* infection recurrence. Zinplava is not indicated for the treatment of *Clostridium difficile* infection. Zinplava is not an antibacterial drug, and it should only be used in conjunction with antibacterial drug treatment of *Clostridium difficile* infection. The recommended dose of Zinplava is 10 mg/kg administered one time as an intravenous infusion over 60 minutes.

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***Clostridium difficile* Infection**

Clostridium difficile is an anaerobic gram positive, spore forming, toxin-producing bacillus that is transmitted through the oral-fecal route. This pathogen is commonly found in healthcare facilities. Typically, colonization is prevented by the barrier properties of fecal microbiota, however disruption of the normal gastrointestinal flora by antibiotics in the major cause of *Clostridium difficile* infection. Currently, two oral antibiotics are FDA approved for the treatment of *Clostridium difficile* infection, Dificid®‡ (fidaxomicin) and vancomycin. Metronidazole is also commonly used for the treatment of *Clostridium difficile* infection even though it is not technically FDA approved for the indication. Recommended treatments for recurrent CDI in adults include Dificid and oral vancomycin for first recurrences with Zinplava being an adjunctive agent and Dificid, oral vancomycin, or fecal microbiota transplantation (FMT) for second and subsequent recurrences, with Zinplava again being recommended as an adjunctive agent. For pediatric patients, the recommended treatment for first recurrence, mild or moderate cases, is to repeat the regimen used for the first episode. For subsequence recurrence, either vancomycin or fidaxomicin is recommended. Zinplava is the first drug FDA approved to reduce the recurrence of *Clostridium difficile* infection. Two fecal microbiota products are currently FDA approved, Reybota and Vowst, to prevent the recurrence of CDI in individuals 18 years of age and older. Zinplava has not been studied in combination with FMT for reducing the recurrence of CDI.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zinplava is a human monoclonal antibody that binds to *Clostridium difficile* toxin B and is indicated to reduce the recurrence of *Clostridium difficile* infection in patients 18 years of age or older who are receiving antibacterial drug treatment of *Clostridium difficile* infection and are at high risk for *Clostridium difficile* infection recurrence. Zinplava was FDA approved in October of 2016, and in May 2023, Zinplava's approval expanded to include pediatric patients 1 year of age and older.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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Zinplava was initially evaluated in two randomized, double-blind, placebo controlled trials in patients receiving standard of care antibiotics for the treatment of *Clostridium difficile* infection. In the first trial, adults with a primary or recurrent *Clostridium difficile* infection receiving standard of care antibiotics along with Zinplava demonstrated a lower recurrence of *Clostridium difficile* infection vs. those on standard of care antibiotics plus placebo (17% vs. 28%, respectively, $p<0.001$). In the second trial, similar results were reported. The recurrence of *Clostridium difficile* infection was lower in the Zinplava group compared to the placebo group (16% vs. 26%, $p<0.001$).

A post hoc analysis (based on data on file at Merck) of *Clostridium difficile* infection recurrence in subgroups with a history of at least one *Clostridium difficile* infection episode in the previous 6 months and at least one additional risk factor [≥65 years of age, severe *Clostridium difficile* infection (via a ZAR score of at least 2), or an immunocompromised patient) demonstrated that the use of Zinplava resulted in absolute risk reduction rates of at least 20% (versus lower absolute reduction rates reported in the trials mentioned above). It should be noted that this post hoc analysis was not powered to show significance, however these results provide guidance in narrowing the use of this drug to those who would most likely benefit from its effects due to the absence of a standard definition of "high risk for *Clostridium difficile* infection recurrence."

The safety and pharmacokinetics of Zinplava were evaluated in pediatric patients 1 year of age and older in one randomized, double-blind, placebo-controlled, multi-center trial (MODIFY III). Patients had a diagnosis of CDI and received standard of care treatment with vancomycin, metronidazole, or fidaxomicin for the baseline CDI episode. Patients were randomized 3:1 to receive a single infusion of bezlotoxumab (10 mg/kg) or placebo and were stratified by age at randomization (cohort 1: 12 to <18 years, cohort 2: 1 to <12 years). A total of 143 patients were included in the study with 107 participants receiving Zinplava and 36 receiving a placebo infusion. The primary objective was to characterize bezlotoxumab pharmacokinetics to support dose selection for pediatric patients, and the primary endpoint was the area under the bezlotoxumab serum concentration-time curve (AUC0-inf). The adverse reactions and the pharmacokinetics observed in pediatric patients were comparable to that observed in adults.

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References

1. Zinplava [package insert]. Merck and Company, Incorporated. Whitehouse Station, New Jersey. Updated May 2023.
2. Medical Information Response via Merck. March 24, 2017.
3. Zinplava Drug Evaluation. Express Scripts. Updated January 2017.
4. Sferra TJ, Merta T. Double-Blind, Placebo-Controlled Study of Bezlotoxumab in Children Receiving Antibacterial Treatment for *Clostridioides difficile* Infection (MODIFY III). J Pediatric Infect Dis Soc. 2023 Jun 30;12(6):334-341.
5. Johnson S, Lavergne V., 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.
6. McDonald LC, Gerding DN, 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.

Policy History

Original Effective Date: 05/17/2017
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05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. New Policy.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. No change to coverage.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. No change to coverage.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. No change to coverage.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. No change to coverage.
05/04/2023	Medical Policy Committee review

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05/10/2023 Medical Policy Implementation Committee approval. No change to coverage.
05/02/2024 Medical Policy Committee review
05/08/2024 Medical Policy Implementation Committee approval. Updated criteria to reflect FDA approval in pediatric patients 1 year of age and older and to include WBC and serum creatinine levels as evidence for high risk of CDI recurrence. Added criteria requiring that Zinplava will not be used in combination with fecal microbiota products.
Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0565
ICD-10 Diagnosis	A04.71, A04.72

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.