MEDICAL POLICY

POLICY TITLE	BEZLOTOXUMAB (ZINPLAVA®)
POLICY NUMBER	MP-2.349

Original Issue Date (Created):	**2/1/2018**	
Most Recent Review Date (Revised):	**7/2/2020**	
Effective Date:	**2/1/2021**	**RETIRED**

I. POLICY

Bezlotoxumab (Zinplava®) may be considered **medically necessary** to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older when **all** the following criteria are met:

- Bezlotoxumab (Zinplava®) is prescribed by, or in consultation with a practitioner specializing in Infectious Disease or gastroenterology ; **and**
- *Clostridium difficile (C. difficile)* has been confirmed by a documented positive test for *C. difficile* from a stool sample collected no more than 7 days prior*;* **and**
- Patient has had at least two episodes of CDI reoccurrence (3 episodes) in the past six months which were treated with appropriate treatment for CDI, including a pulsed regimen of vancomycin; **and**
- Patient is at a high risk for CDI recurrence (see Policy Guidelines);
- Patient is currently receiving or will receive concomitant antibacterial drug treatment for CDI (e.g. fidaxomicin, metronidazole, vancomycin).

Repeat administration of bezlotoxumab (Zinplava®) is considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this medication for repeat dosing.

All other indications for bezlotoxumab (Zinplava®) are considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this medication for all other indications.

POLICY GUIDELINES

There is an absence of a standard definition of "high risk for Clostridium difficile infection recurrence." However, the following are examples that provide guidance in narrowing the use of this drug to those who would most likely benefit from its effects:

- Aged 65 or older; or

- Immunocompromised (e.g., having an active hematologic malignancy, using corticosteroids or antineoplastic agents, transplant recipient, asplenic, AIDS or immunodeficient condition); or
- Patient has severe Clostridium difficile infection as evidenced by a ZAR score* of greater than or equal to 2

*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)

Cross-reference:

MP-2.103 Off-Label Use of Medications

II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Benefit Brochure for information on BEZLOTOXUMAB (ZINPLAVA®) https://www.fepblue.org/benefit-plans/benefit-plans-brochures-and-forms.

Note* - The Federal Employee Program (FEP) Service Benefit Plan does not have a medical policy related to these services.

Note for Medicare Advantage Products:

FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice." Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug). *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

1. In accordance with CMS letter issued on September 17, 2012, entitled "Prohibition on Imposing Mandatory Step Therapy for Access to Part B Drugs and Services". Step therapy that is not part of the FDA label does not apply to Medicare Advantage.

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III. DESCRIPTION/BACKGROUND

TOP

Clostridium difficile infection (CDI) is caused by bacteria that produce toxins, including toxin B. Symptoms of CDI include mild-to-severe diarrhea, abdominal pain and fever (Merck, 2016).

In October 2016, The US Food and Drug Administration (FDA) approved bezlotoxumab injection (*Zinplava*, Merck) to reduce the recurrence of *Clostridium difficile* infection (CDI) in patients aged 18 years or older. The human monoclonal antibody is specifically indicated for adults who are taking an antibiotic for CDI and are at risk of becoming infected again. Not an antibiotic itself, bezlotoxumab binds to and neutralizes toxin B, one of several toxins produced by *C difficile* and the one considered central to the life-threatening virulence of the bacteria. Bezlotoxumab is administered intravenously (IV) as a single dose of 10 mg/kg over 1 hour. The labeling states that the safety and efficacy of repeat administration of bezlotoxumab in patients with CDI have not been studied.

Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10–14 days. Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10–14 days. Vancomycin administered orally (and per rectum, if ileus is present) with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every 8 hours. Treatment of the second or later recurrence of CDI with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy.

IV. RATIONALE

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For information on clinical studies for bezlotoxumab (Zinplava®) refer to Prescribing Information.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and

providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary in patients 18 years of age or older:

HCPCS Codes	Description
J0565	Injection, bezlotoxumab, 10 mg

ICD-10-CM Diagnosis Code	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent

IX. REFERENCES

TOP

1. *Antimicrobial Drugs Advisory Committee. Bezlotoxumab injection briefing document (BLA 761046). Published June 9, 2016. [Website]: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm505290.pdf . Accessed July 1, 2020.*
2. *McDonald, L, Gerding D. 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) https://academic.oup.com/cid/article/66/7/e1/4855916 Accessed July 1, 2020.*

3. *Merck & Co., Inc. FDA approves Merck's Zinplava (bezlotoxumab) to reduce recurrence of Clostridium difficile infection (CDI) in adult patients receiving antibacterial drug treatment for CDI who are at high risk of CDI recurrence. Press Release. Kenilworth, NJ: Merck; October 21, 2016.*
4. *National Guideline Clearinghouse (NGC). Guideline summary: Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. In: National Guideline Clearinghouse (NGC) [Website]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Apr 01. [cited 2017 Jun 05]. Available: https://guideline.gov Accessed July 1, 2020..*
5. *Zinplava Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc; October 2016. [Website]: http://www.merck.com/product/usa/pi_circulars/z/zinplava/zinplava_pi.pdf Accessed July 1, 2020.*

X. POLICY HISTORY

TOP

MP-2.349	**9/26/17 CAC** New policy. Bezlotoxumab (Zinplava) may be considered medically necessary for the treatment of *Clostiridium difficile* when specific policy criteria are met. Coding reviewed.
	6/4/18 Consensus. No change to policy statements. References updated.
	4/16/19 Consensus. No change to policy statements. References updated.
	7/2/2020 Consensus Review. Policy Statement unchanged. Product Variation Statement updated. Coding checked with no changes. References reviewed and updated. FEP statement added.

Top