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Criteria for Formulary Consideration of bezlotoxumab (Zinplava™)

Efficacy[4,7,9]

Bezlotoxumab (Zinplava™) is a human monoclonal antibody approved by the FDA in October 2016 to reduce the recurrence of *Clostridium difficile* 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. Bezlotoxumab prevents recurrence by binding to C. *difficile* toxin B and neutralizes its effects. Bezlotoxumab is not an antibacterial drug and not indicated for the treatment of CDI. Bezlotoxumab should only be used in conjunction with antibacterial drug treatment of CDI.

Debilitating symptoms of CDI are caused by two exotoxins – *C. difficile* toxins A and B. Clinical trials have shown that neutralization of these toxins can prevent recurrence of infection, offering an antibacterial-sparing treatment option. Preclinical data suggest that this approach allows the gut microbiota to recover. Bezlotoxumab was developed in conjunction with actoxumab, a monoclonal antibody against *C. difficile* toxin A. Neutralization of both toxins was originally thought to provide optimal therapeutic benefit; however, the phase III MODIFY I and MODIFY II trails did not demonstrate additional therapeutic benefit in patients who received actoxumab.

The MODIFY I and II trials assessed the efficacy and safety of bezlotoxumab alone and in combination of actoxumab for the prevention of CDI recurrence in adults receiving antibiotic treatment for primary or recurrent CDI. The actoxumab arm of the MODIFY I trial was dropped from further study following interim analysis due to lack of efficacy and higher rate of serious adverse events and death compared with placebo. In both studies, bezlotoxumab was superior to placebo in prevention of CDI recurrence over 12 weeks (p=0.0003 for MODIFY I and II) and had a safety profile similar to placebo. Recurrence rates with bezlotoxumab were 17.4% and 15.7% in MODIFY I and II, respectively compared to 26.7% and 25.7%, respectively with placebo. In the pooled analysis, bezlotoxumab was associated with a 10% absolute reduction in CDI recurrence versus placebo overall. Patient risk factors for CDI recurrence or CDI-related adverse outcomes included: age ≥65 years, history of CDI, compromised immunity, clinically severe CDI (Zar score ≥2), or an infection with a strain associated with poor outcomes (027, 078, or 244).

Safety[7]

Heart failure was reported more commonly in bezlotoxumab-treated patients with a history of congestive heart failure (CHF) in the two Phase III clinical trials. Bezlotoxumab should be reserved for use when the benefit outweighs the risk in patients with a history of CHF. The most common adverse reactions included nausea, pyrexia, and headache (reported in ≥4% of patients). The safety and efficacy of repeat administration of bezlotoxumab after a single dose in patients with CDI have not been studied.

Uniqueness[7]

- Bezlotoxumab is the first approved agent indicated to reduce the recurrence of *C. difficile.*
- Bezlotoxumab is administered during antibacterial drug treatment for CDI and administered as a single dose intravenous infusion.

Cost[8]

IV Solution: 1000 mg/40 mL (40 mL): $4560.00 AWP

Recommendations

Add bezlotoxumab to outpatient infusion center formulary.

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

Introduction[1-4, 6, 7]

C. *difficile* is the leading cause of health care-associated infections. Patients with CDI have increased length of hospital stay, higher readmission rates, more elevated inpatient costs, and higher mortality rates than patients without CDI. A frequent precursor to C. *difficile* proliferation is an alteration of the normal GI flora, commonly the result of antibiotic use. Once CDI is diagnosed, the associated antibiotics should be stopped as soon as possible, as clinically indicated. Further courses of antibacterial drugs to treat CDI prevent re-establishment of the gut microbiota and may lead to multiple recurrences of CDI. Although antibiotic treatment of primary CDI is often successful, up to 35% of patients experience CDI recurrence after completing initial antibiotic therapy. After first recurrence, patients have a 45% probability of a second recurrence, with the risk increasing with further recurrences.

Guidelines offering guidance on the treatment of CDI include: the 2010 guidelines of the Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) – whose updated version is currently under progress; the 2013 guidelines of the American College of Gastroenterology (ACG); and the 2014 guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Table 1 summarizes the pharmacological treatment recommendations for those guidelines.

CDI recurrence is defined as a reappearance of documented CDI either within 8 weeks of completion of anticlostridial treatment, or within the 8 weeks following the onset of the first episode. Risk factors for CDI recurrence include: age over 65 years, continued use of antibiotics after CDI diagnosis, severe comorbidity including renal failure, one previous CDI episode, use of proton pump inhibitors, and severe initial CDI. The majority of guidelines recommend using the same antibiotic in a second CDI episode that had been previously prescribed for the first one with reasonable adjustments according to disease severity.

Table 1. Summary of pharmacological treatment recommendations of CDI guidelines[1-3,6]

	IDSA/SHEA 2010	ACG 2013	ESCMID 2014
First Episode			
Mild – Moderate	Metronidazole 500 mg po q 8 hr x 10-14 days *(A-I)*	Metronidazole 500 mg po q 8 hr x 10 days *(strong/moderate)* Vancomycin 125 mg po q 6 hr x 10 days (in case of no response after 5-7 days of metronidazole therapy *(strong/moderate),* metronidazole intolerance/allergy, or pregnant/breastfeeding *(strong/high))* Add vancomycin 500 mg (in 100-500 mL of NS) q 6 hr via enemas if oral antibiotics cannot reach segment of the colon *(conditional/low)*	Metronidazole 500 mg po q 8 hr x 10 days *(A-I)* Vancomycin 125 mg po q 6 hr x 10 days *(B-I)* (preferred over metronidazole if risk of recurrence) Fidaxomicin 200 mg po q 12 hr x 10 days *(B-I)* (preferred over metronidazole if risk of recurrence) Metronidazole 500 mg IV q 8 hr x 10 days if intolerance of oral treatment *(A-II)* Stop systemic antibiotics + 48 hr clinical observation *(C-II)* Immunotherapy with human monoclonal antibodies *(C-I)* or immune whey *(C-II)*

Severe	Vancomycin 125 mg po q 6 hr x 10-14 days *(B-I)*	Vancomycin 125 mg po q 6 hr x 10 days *(conditional/moderate)* Add vancomycin 500 mg (in 100-500 mL of NS) q 6 hr via enemas if oral antibiotics cannot reach segment of the colon *(conditional/low)*	Vancomycin 125 mg po q 6 hr x 10 days *(A-I)* Fidaxomicin 200 mg po q 12 hr x 10 days *(B-I)* Metronidazole 500 mg IV q 8 hr x 10 days *(A-II)* + vancomycin 500 mg (in 100 mL NS) q 6 hr via enemas or NGT x 10 days if oral treatment not possible *(B-III)* Tigecyline 50 mg IV q 12 hr x 14 days if oral treatment not possible *(C-III)*
Severe complicated	Vancomycin 500 mg po/NGT q 6 hr + metronidazole 500 mg IV q 8 hr Consider adding vancomycin 500 mg (in 100-500 mL of NS) q 6 hr via enemas if ileus is present *(C-III)*	Vancomycin 125 mg po q 6 hr + metronidazole 500 mg IV q 8 hr *(strong/low)* Vancomycin 500 mg po q 6 hr + 500 mg (in 100-500 mL of NS) via enemas + metronidazole 500 mg IV q 8 hr if ileus or significant abdominal distension is present *(strong/low)*	DO NOT use metronidazole in monotherapy *(D-I)*
	IDSA/SHEA 2010	ACG 2013	ESCMID 2014
First Recurrence	Same treatment as for initial episode stratified according to disease severity *(C-III)*	Same treatment as for initial episode stratified according to disease severity	Vancomycin 125 mg po q 6 hr x 10 days *(B-I)* Fidaxomicin 200 mg po q 12 hr x 10 days *(B-I)* Metronidazole 500 mg po q 8 hr x 10 days *(C-I)*
Multiple Recurrences	Vancomycin 125 mg po q 6 hr x 10-14 days followed by a tapering and/or pulsed regimen of po vancomycin *(B-III)*	2nd recurrence: Vancomycin 125 mg po q 6 hr x 10 days followed by a pulsed regimen of po vancomycin *(conditional/low)* ≥3rd recurrence: Consider intestinal microbiota transplant *(conditional/moderate)*	Intestinal microbiota transplantation after 4 days of vancomycin 500 mg po q 6 hr *(A-I)* Vancomycin 125 mg po q 6 hr x 10 days, followed by a tapering or pulsed regimen of po vancomycin *(B-II)* Vancomycin 500 mg po q 6 hr x 10 days *(C-II)* DO NOT use metronidazole in monotherapy *(D-II)*

Pharmacokinetics[7]

The clearance of bezlotoxumab increased with increasing body weight; the resulting exposure differences are adequately addressed by the administration of a weight-based dose. Bezlotoxumab is eliminated by catabolism.

Table 2. Geometric Mean Based on a Population PK Analysis of 1515 CDI Patients in Two Phase 3 Trials[7]

Clearance (L/day)	Volume of Distribution (L)	Elimination Half-Life (days)	AUC0-INF (mcg•h/mL)	Cmax (mcg/mL)
0.317 (41%)	7.33 (16%)	19 (28%)	53000	185

Patients with Renal Impairment
The effect of renal impairment on the pharmacokinetics of bezlotoxumab was evaluated in patients with mild (eGFR 60 to <90 mL/min/1.73 m2), moderate (eGFR 30 to <60 mL/min/1.73 m2), or severe (eGFR 15 to <30 mL/min/1.73 m2) renal impairment, or with end stage renal disease (eGFR <15 mL/min/1.73 m2), as compared to patients with normal (eGFR ≥90 mL/min/1.73 m2) renal function. No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with renal impairment and patients with normal renal function.

Patients with Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of bezlotoxumab was evaluated in patients with hepatic impairment (defined as having two or more of the following: [1] albumin ≤3.1 g/dL; [2] ALT ≥2X ULN; [3] total bilirubin ≥1.3X ULN; or [4] mild, moderate or severe liver disease as reported by the Charlson Co-morbidity Index), as compared to patients with normal hepatic function. No clinically meaningful differences in the exposure of bezlotoxumab were found between patients with hepatic impairment and patients with normal hepatic function.

Geriatric Patients
The effect of age on the pharmacokinetics of bezlotoxumab was evaluated in patients ranging from 18 to 100 years of age. No clinically meaningful differences in the exposure of bezlotoxumab were found between patients ≥65 years and patients <65 years of age.

Pharmacology[7]

Bezlotoxumab is a human monoclonal antibody that binds to C. *difficile* toxin B and neutralizes its effects. Bezlotoxumab does not bind to *C. difficile* toxin A.

FDA Approved Indications[7]

Bezlotoxumab (Zinplava™) is indicated to reduce 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. Bezlotoxumab (Zinplava™) was approved on October 21, 2016.

Clinical Trials[4,7,9]

Table 3. MODIFY I Trial[4,6]

Study Design	Methods	Results	Conclusions/Comments
Wilcox et al Randomized, double-blind, place controlled, multi-center phase 3 trial 1452 patients enrolled 403 patients randomized to receive bezlotoxumab 404 patient randomized to receive placebo	*Inclusion Criteria* • 18 years of age and older • Confirmed diagnosis of CDI (diarrhea passage of 3 or more loose bowel movements in 24 or fewer hours, and a positive stool test for toxigenic C. *difficile* from a stool sample collected no more than 7 days before study entry) *Exclusion Criteria* • Surgery for CDI planned • Uncontrolled chronic diarrheal illness	*Efficacy Outcomes* **CDI Recurrence⊥:** • 61 (15.9%, p<0.0001) patients in actoxumab+bezlotoxumab group o NNT=9 • 60 (25.9%) patients in actoxumab group • 67 (17.4%, p=0.0003) patients in bezlotoxumab group o NNT=10 • 109 (27.6%) patients in placebo group **Sustained Clinical Response* (Global Cure Rate):**	*Author's Conclusion:* • Recurrent CDI rates were significantly lower for actoxumab+bezlotoxumab, and bezlotoxumab monotherapy groups vs placebo. • Global cure rates were higher for actoxumab+bezlotoxumab, and for bezlotoxumab alone vs placebo. • Treatment with actoxumab+bezlotoxumab did

Patients received a 10-14 day course of oral SoC‡ and a single infusion during the course of SoC‡ of one of the following: -actoxumab + bezlotoxumab 10 mg/kg each -actoxumab 10 mg/kg -bezlotoxumab 10 mg/kg -placebo Patients on oral vancomycin or oral fidaxomicin could have also received intravenous metronidazole. Choice of SoC‡ was at the discretion of the health care provider. Randomization was stratified by SoC‡ and hospitalization status† at the time of study entry 12 week study period		• 225 (58.7%, p=0.16) patients in actoxumab+bezlotoxumab group • 109 (47%) patients in actoxumab group • 232 (60.1%, p=0.09) patients in bezlotoxumab group • 218 (55.2%) patients in placebo group 95% CI 4.8 (-2.1, 11.7) **Clinical Failure:** • 22.5% patient in bezlotoxumab group • 17.2% patients in placebo group *Adverse Events* • Comparable in all groups with the most common adverse reactions included nausea, diarrhea, and pyrexia through 4 weeks • 2-fold increase in serious adverse events and deaths were reported with actoxumab monotherapy; this treatment was terminated for efficacy and safety reasons following an interim analysis Median age: 65 years, ~55% were female The day of the infusion of bezlotoxumab or placebo in relation to the start of SoC‡ ranged from the day prior to the start of SoC‡ to 14 days after the start of SoC‡ with the median being day 3 of SoC‡ A similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) and 4% of the patients received oral fidaxomicin as their SoC‡	not provide added efficacy over bezlotoxumab monotherapy. • Actoxumab alone provided no benefit in the prevention of C. *difficile* recurrence compared to placebo.

‡ SoC = Standard of Care antibacterial drugs (metronidazole or vancomycin or fidaxomicin) for CDI for 10-14 days
† Inpatient vs. outpatient
⊥ CDI recurrence, defined as development of a new episode of diarrhea associated with a positive stool test for toxigenic C. *difficile* following clinical cure of presenting CDI episode through week 12
* Sustained clinical response, defined as defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion

Table 4. MODIFY II Trial[4,7,9]

Study Design	Methods	Results	Conclusions/Comments
Gerding et al Randomized, double-blind, place controlled, multi-center phase 3 trial 1203 patients enrolled 407 patients randomized to receive bezlotoxumab 399 patients randomized to receive placebo Patients received a 10-14 day course of oral SoC‡ and a single infusion during the course of SoC‡ of one of the following:	*Inclusion Criteria* • 18 years of age and older • Confirmed diagnosis of CDI (diarrhea passage of 3 or more loose bowel movements in 24 or fewer hours, and a positive stool test for toxigenic C. difficile from a stool sample collected no more than 7 days before study entry) *Exclusion Criteria* • Surgery for CDI planned • Uncontrolled chronic diarrheal illness	*Efficacy Outcomes* **CDI Recurrence⊥:** • 58 (14.9%, p<0.0001)) patients in actoxumab+bezlotoxumab group o NNT=9 • 62 (15.7%. p=0.0003) patient in bezlotoxumab group o NNT=10 • 97 (25.7%) patients in placebo group **Sustained Clinical Response*(Global Cure Rate):** • 224 (57.4%, p=0.072) of patients in actoxumab+bezlotoxumab group • 264 (66.8%, p<0.0001) patients in bezlotoxumab group	*Author's Conclusion:* • Recurrent CDI rates were significantly lower for actoxumab+bezlotoxumab, and for bezlotoxumab monotherapy groups vs placebo • Global cure rate was superior for bezlotoxumab alone, and higher for actoxumab+bezlotoxumab vs placebo

-actoxumab + bezlotoxumab 10 mg/kg each -bezlotoxumab 10 mg/kg -placebo Patients on oral vancomycin or oral fidaxomicin could have also received intravenous metronidazole. Choice of SoC‡ was at the discretion of the health care provider. Randomization was stratified by SoC‡ and hospitalization status† at the time of study entry 12 week study period		• 197 (52.1%) patients in placebo group 95% CI 14.6 (7.7, 21.4) **Clinical Failure:** • 17.5% patient in bezlotoxumab group • 22.2% patients in placebo group *Adverse Events* • Comparable in all groups with the most common adverse reactions included nausea, diarrhea , and urinary tract infection through 4 weeks Median age: 67 years, ~55% were female The day of the infusion of bezlotoxumab or placebo in relation to the start of SoC‡ ranged from the day prior to the start of SoC‡ to 14 days after the start of SoC‡ with the median being day 3 of SoC‡ A similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) and 4% of the patients received oral fidaxomicin as their SoC‡	

‡ SoC = Standard of Care antibacterial drugs (metronidazole or vancomycin or fidaxomicin) for CDI for 10-14 days
† Inpatient vs. outpatient
⊥ CDI recurrence, defined as development of a new episode of diarrhea associated with a positive stool test for toxigenic C. *difficile* following clinical cure of presenting CDI episode through week 12
* Sustained clinical response, defined as defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion

Table 5. Efficacy Results Through 12 Weeks After Infusion (Trial 1 and Trial 2, Full Analysis Set≠)[7]

Trial	**Bezlotoxumab with SoC‡** n (%)	**Placebo with SoC‡** n (%)	**Adjusted Difference** (95% CI)
1	N=386	N=395	
Sustained clinical response*	232 (60.1)	218 (55.2)	4.8 (-2.1, 11.7)
Reasons for failure to achieve sustained clinical response:			
Clinical failure	87 (22.5)	68 (17.2)	
CDI Recurrence⊥	67 (17.4)	109 (27.6)	
2	N=395	N=378	
Sustained clinical response*	264 (66.8)	197 (52.1)	14.6 (7.7, 21.4)
Reasons for failure to achieve sustained clinical response:			
Clinical failure	69 (17.5)	84 (22.2)	
CDI Recurrence⊥	62 (15.7)	97 (25.7)	

≠ Full Analysis Set = a subset of all randomized subjects with exclusions for: (i) did not receive infusion of study medication; (ii) did not have a positive local stool test for toxigenic *C. difficile;* (iii) did not receive protocol defined standard of care therapy within a 1 day window of the infusion
‡ SoC = Standard of Care antibacterial drugs (metronidazole or vancomycin or fidaxomicin) for CDI

* Sustained clinical response, defined as defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion
⊥ CDI recurrence, defined as development of a new episode of diarrhea associated with a positive stool test for toxigenic C. *difficile* following clinical cure of presenting CDI episode

Efficacy results in patients at high risk for CDI recurrences (i.e., patients aged ≥65 years, with a history of CDI in past 6 months, immunocompromised state, severe CDI at presentation, or C. difficile ribotype 027) were consistent with the efficacy results in the overall trial population in Trials 1 and 2.

Warnings, Precautions, and Adverse Effects[7]

Safety and efficacy of bezlotoxumab in patients below 18 years of age have not been established. The safety and efficacy of repeat administration of bezlotoxumab in patients with CDI have not been studied.

Warnings and Precautions
Heart failure was reported more commonly in bezlotoxumab-treated patients with a history of congestive heart failure (CHF) in the two Phase 3 clinical trials. 12.7% (15/118) of bezlotoxumab-treated patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure during the 12-week study period. Additionally, in patients with a history of CHF, there were more deaths in bezlotoxumab-treated patients, 19.5% (23/118) than in placebo-treated patients, 12.5% (13/104) during the 12-week study period. The causes of death varied and included cardiac failure, infections, and respiratory failure. In patients with a history of CHF, bezlotoxumab should be reserved for use when the benefit outweighs the risk.

As with all therapeutic proteins, there is a potential for immunogenicity following administration of bezlotoxumab. Following treatment with bezlotoxumab in Trial 1 and Trial 2, none of the 710 evaluable patients tested positive for treatment-emergent anti-bezlotoxumab antibodies.

Adverse Effects
The most common adverse reactions (reported in ≥4% of patients) included nausea, pyrexia, and headache.
Table 6 summarizes the adverse reactions reported within the first 4 weeks after bezlotoxumab was administered are described for the pooled Phase 3 trial population of 786 patients.

Table 6. Adverse Reactions Reported in ≥4% of Bezlotoxumab-Treated Patients with CDI and at a Frequency Greater than Placebo in Trial 1 and Trial 2[*,+,7]

Adverse Reaction	Bezlotoxumab with SoC‡ N=786	Placebo with SoC‡ N=781
Nausea	7%	5%
Pyrexia	5%	3%
Headache	4%	3%

* All patients as treated population, defined as all randomized patients who received a dose of study medication, by treatment received
+ Adverse reactions reported within 4 weeks of administration of bezlotoxumab or placebo
‡ SoC = Standard of Care antibacterial drugs (metronidazole or vancomycin or fidaxomicin) for CDI

One patient discontinued bezlotoxumab infusion due to ventricular tachyarrhythmia that occurred 30 minutes after the start of the infusion. Mortality rates were 7.1% and 7.6% in ZINPLAVA-treated patients and placebo-treated patients, respectively, during the 12-week follow-up period.

Infusion Related Reactions
Overall, 10% of bezlotoxumab-treated patients experienced one or more infusion specific adverse reactions on the day of, or the day after, the infusion compared to 8% of placebo-treated patients. Infusion specific adverse reactions reported in ≥0.5% of patients receiving ZINPLAVA and at a frequency greater than placebo were nausea (3%), fatigue (1%), pyrexia (1%), dizziness (1%), headache (2%), dyspnea (1%) and hypertension (1%). Of these patients, 78% and 20% of patients experienced mild and moderate adverse reactions, respectively. These reactions resolved within 24 hours following onset.

Pregnancy and Lactation
Adequate and well controlled studies with bezlotoxumab have not been conducted in pregnant women. No animal reproductive and developmental studies have been conducted with bezlotoxumab. The background risk of major birth

defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.
There is no information regarding the presence of bezlotoxumab in human milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bezlotoxumab and any potential adverse effects on the breastfed child from bezlotoxumab or from the underlying maternal condition.

Interactions[7]

Since bezlotoxumab is eliminated by catabolism, no metabolic drug-drug interactions are expected.

Dosage and Administration[7]

Administer bezlotoxumab during antibacterial drug treatment for CDI. The recommended dose is a single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes. Administer the diluted solution as an intravenous infusion using a sterile, nonpyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. The diluted solution can be infused via a central line or peripheral catheter. Do not administer as an intravenous push or bolus. Do not co-administer other drugs simultaneously through the same infusion line.

Monitoring Parameters

No monitoring recommendations reported.

How Supplied/Cost[7,8]

IV Solution
1000 mg/40 mL (40 mL): $4560.00

Bezlotoxumab injection is a sterile, preservative-free, clear to moderately opalescent, colorless to pale yellow solution and is supplied in the following packaging configuration: Carton (NDC 0006-3025-00) containing one (1) single-dose vial of ZINPLAVA 1,000 mg/40 mL(25mg/mL). The product is provided in a 50 mL vial that contains 1000 mg of bezlotoxumab in 40 mL of solution. Each mL of solution contains bezlotoxumab (25 mg), citric acid monohydrate (0.8 mg), diethylenetriaminepentaacetic acid (0.0078 mg), polysorbate 80 (0.25 mg), sodium chloride (8.77 mg), sodium citrate dihydrate (4.75 mg), and Water for Injection, USP. The vial may contain sodium hydroxide to adjust the pH to 6.0.

Preparation of Diluted Solution
Must be diluted prior to intravenous infusion. Prepare the diluted solution immediately after removal of the vial(s) from refrigerated storage, or the vial(s) may be stored at room temperature protected from light for up to 24 hours prior to preparation of the diluted solution. Inspect vial contents for discoloration and particulate matter prior to dilution. Bezlotoxumab is a clear to moderately opalescent, colorless to pale yellow solution. Do not use the vial if the solution is discolored or contains visible particles. Do not shake the vial. Withdraw the required volume from the vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard vial(s) and all unused contents.

Storage of Diluted Solution
The product does not contain preservative. The diluted solution may be stored either at room temperature for up to 16 hours or under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 24 hours. If refrigerated, allow the intravenous bag to come to room temperature prior to use. These time limits include storage of the infusion solution in the intravenous bag through the duration of infusion. Do not freeze the diluted solution.

Administration
Administer the diluted solution as an intravenous infusion over 60 minutes using a sterile, nonpyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. The diluted solution can be infused via a central line or peripheral catheter. Do not administer as an intravenous push or bolus. Do not co-administer other drugs simultaneously through the same infusion line.

Pharmacoeconomic Analysis[5]

- A computer-based Markov health state transition model was developed to stimulate the natural history of CDI.
- In the model, patients with CDI were followed from infection until death and evaluated the costs and effectiveness of bezlotoxumab+SoC compared with placebo+SoC using a third-party payer perspective.
- To evaluate cost-effectiveness in different patient population, analysis was conducted for the entire clinical trial population (subgroup 1), and for CDI patients at higher risk of rCDI—age 65 years and above and having a history of CDI (subgroup 2).
- Recurrence rates after infusion for bezlotoxumab and placebo were taken directly from the pooled MODIFY I & II phase III clinical trials' efficacy data. Other transition probabilities and costs of rCDI were obtained from the literature. Projection on rCDI averted, discounted age-weighted quality-adjusted life years (QALYs), and threshold prices at which bezlotoxumab would be cost-effective at the $100,000/QALY threshold was made.
- The model predicted that treating patients with bezlotoxumab+SoC will reduce the combined incidence of first, second, and third CDI recurrences after infusion by 16.4% and 39.4% in subgroup 1 and subgroup 2, respectively. This resulted in 0.16 and 0.28 incremental discounted age-weighted QALYs gained per-patient for subgroup 1 and subgroup 2, respectively. The threshold price at which bezlotoxumab is cost-effective at the $100,000/QALY threshold is $17,188 and $30,118 for subgroup 1 and subgroup 2, respectively. Key influential parameters include CDI-specific mortality, cost of a rCDI episode, and underlying recurrence rate.
- Based on the Markov model, bezlotoxumab has the potential to reduce the disease burden associated with CDI in a cost-effective manner, by reducing the incidence of rCDI.

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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations[1-4,6,7]

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Bezlotoxumab (Zinplava™)
Drug manufacturer	Merck & Co.
Schedule of medication	Rx
Anticipated use per month, anticipated patient population	3
Route of administration	Intravenous
Preparation	Dilute prior to intravenous infusion. Prepare the diluted solution immediately after removal of the vial(s) from refrigerated storage, or the vial(s) may be stored at room temperature protected from light for up to 24 hours prior to preparation of the diluted solution. Inspect vial contents for discoloration and particulate matter prior to dilution. Bezlotoxumab is a clear to moderately opalescent, colorless to pale yellow solution. Do not use the vial if the solution is discolored or contains visible particles. Do not shake the vial. Withdraw the required volume from the vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard vial(s) and all unused contents.
Stability	The diluted solution of bezlotoxumab may be stored either at room temperature for up to 16 hours or under refrigeration up to 24 hours.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Does not contain preservative. The diluted solution of bezlotoxumab may be stored either at room temperature for up to 16 hours or under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 24 hours. If refrigerated, allow the intravenous bag to come to room temperature prior to use. These time limits include storage of the infusion solution in the intravenous bag through the duration of infusion. Do not freeze the diluted solution.
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	

Is filtration required during preparation or administration of the IV medication?	No ☒ Yes ☐ N/A ☐
Can medication doses be sent to patient care units via pneumatic tube system? See IC24.	No ☒ Yes ☐ N/A ☐
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any black box warning? For what?	No ☒ Yes ☐
Is this medication a hazardous agent?	No ☒ Yes ☐
Is the medication a vesicant or irritant?	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02.	No ☒ Yes ☐
Are there contraindications or significant warnings against medication use?	No ☐ Yes ☒
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☐ Yes ☒
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Will the medication be restricted: MS68 Levels of Care • To a specific level of care (LOC)? • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	 No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐

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