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Drug Class Update with New Drug Evaluation: Medications for *Clostridium difficile* Infection

Date of Review: May 2018
Generic Name: Bezlotoxumab Infusion
PDL Class: Clostridium Difficile Antibiotics

Date of Last Review: May 2015
Literature Search: 01/01/2015 – 03/14/18
Brand Name (Manufacturer): Zinplava (Merck)
AMCP Dossier Received: Yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Review a new therapy, bezlotoxumab, targeted against *Clostridium difficile* toxin B to reduce the incidence of recurrent *Clostridium difficile* infection (CDI). In addition, any new comparative evidence for existing agents in this class will be reviewed and summarized.

Research Questions:
1. What is the comparative efficacy or effectiveness of metronidazole, vancomycin and fidaxomicin in treating patients with CDI?
2. What are the comparative harms of metronidazole, vancomycin and fidaxomicin when used for CDI treatment?
3. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) for which one antibiotic is more effective or associated with more harm than other antibiotics?

Conclusions:
- Since the last literature scan on antibiotics for CDI, two new systematic reviews were published.[1,2] The Agency for Healthcare Research and Quality (AHRQ) evaluated recent comparative evidence for vancomycin, metronidazole and fidoxamicin.[1] Moderate quality evidence found vancomycin to be more effective than metronidazole for initial cure of CDI in adults.[1] In the prevention of recurrent CDI, moderate quality evidence supported the superior effectiveness of fidaxomicin over vancomycin.[1] A second systematic review from Cochrane reinforced the findings of the AHRQ report. The Cochrane review pooled date from four trials of moderate quality to support vancomycin superiority over metronidazole for achieving resolution of mild to moderate CDI with no relapse.[2] In the pooled analysis, 72% of metronidazole patients achieved symptomatic cure compared to 79% of vancomycin patients (RR 0.90, 95% Confidence Interval (CI) 0.84 to 0.97).[2] Two large studies of moderate quality found fidaxomicin superior to vancomycin in resolving symptoms of CDI.[2] In the Cochrane pooled analysis, 71% of fidaxomicin patients achieved symptomatic cure compared to 61% of vancomycin patients (relative risk [RR] 1.17, 95% CI 1.04 to 1.31).[2]
- The Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) 2017 guideline updates recommend using oral vancomycin or fidaxomicin for an initial CDI episode.[3] Metronidazole is no longer recommended as a first line agent, except in circumstances where access to

vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.[3] The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode of CDI.[3] Metronidazole is not recommended for treatment of recurrent CDI.[3] Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.[3] Fidaxomicin is not FDA-approved for use in children less than 18 years of age, so it is not included in the IDSA/SHEA pediatric recommendations.[3]

- Two phase 3 trials (MODIFY I and MODIFY II) of moderate quality were conducted to evaluate the safety and efficacy of bezlotoxumab, a human monoclonal antibody, in reducing the incidence of recurrent CDI.[4] In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17% vs. 28%; 95% CI, -15.9 to -4.3; p <0.001; MODIFY II: 16% vs 26%; 95% CI, -15.5 to -4.3; p < 0.001).[4] Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg infusion.[5]
- During the 2 clinical trials, the most common adverse reactions occurring with bezlotoxumab within 4 weeks of infusion with a frequency greater than placebo included nausea (7% vs 5%), pyrexia (5% vs 3%) and headache (4% vs 3%).[4] In bezlotoxumab-treated patients, 10% experienced one or more infusion specific adverse reactions compared to 8% of placebo-treated patients.[4] In patients with a history of congestive heart failure [CHF], 12.7% of bezlotoxumab-treated patients and 4.8% of placebo-treated patients had the serious adverse reaction of heart failure exacerbation during the 12-week study period.[4] Additionally, in patients with a history of CHF, there were more deaths in bezlotoxumab-treated patients (19.5%) than in placebo-treated patients (12.5%).[4]

Recommendations:

- Designate bezlotoxumab as a non-preferred drug subject to Prior Authorization.
- Modify fidaxomicin PA criteria to remove metronidazole as a prerequisite to fidaxomicin in patients with recurrent CDI.
- No PDL changes recommended after review of comparative drug costs in executive session.

Previous Conclusions:

- There is moderate strength of evidence oral vancomycin is superior to oral metronidazole for clinical cure of first episode of mild to moderate *Clostridium difficile* infection. There is moderate strength of evidence of no difference between oral vancomycin and oral fidaxomicin in clinical cure rate of first episode of CDI. There is insufficient evidence to compare efficacy between metronidazole and fidaxomicin.
- There is high strength evidence that oral vancomycin is superior to oral metronidazole in severe or complicated CDI but there is insufficient evidence to support the use of fidaxomicin alone for complicated or fulminant CDI.
- There is moderate strength of evidence to repeat the initial antibiotic course for first recurrence of CDI, though moderate quality evidence suggests a course of fidaxomicin is superior to a course of oral vancomycin at preventing further recurrences of CDI. However, following a full-dose course of vancomycin with a slow taper or pulsed dosing over several weeks may also decrease recurrent cases of CDI.
- There is high quality evidence for 10 days of CDI treatment with insufficient evidence to support longer duration of therapy; the exception being pulsed or tapered vancomycin in cases of multiple recurrent CDI that may be given for several weeks after a full dose 10-day course is completed.
- There is insufficient evidence to support the combination of two orally administered antibiotics. Anecdotal evidence, however, suggests intravenous metronidazole or rectal enema administration of vancomycin may be helpful as adjunctive therapy in complicated or fulminant CDI, but never as monotherapy.

Previous Recommendations:

- No further review or research needed at this time. Review comparative drug costs in the executive session.

Background:

CDI has become the most common cause of health care–associated infections in American hospitals, and the additional annual health care costs related to CDI are estimated to be as much as $5.9 billion.[6] The Centers for Disease Control and Prevention (CDC) has identified CDI as a global public health threat due to the emerging prevalence of more virulent *C.difficile* strains and increasing mortality rates due to resistant strains of the bacteria.[7] Community associated CDI is also on the rise and is estimated to occur in one third of all CDI cases.[8] The frequency of recurrent CDI is about 21%.[9] Antibiotic exposure, in particular clindamycin, cephalosporins, and fluoroquinolones increase the risk of developing CDI.[10] All fluoroquinolone antibiotics carry a warning regarding CDI development. Broad spectrum antibiotics reduce normal gut flora which results in *C.difficile* overgrowth in the colon. Other risk factors for CDI include older age, recent hospitalization, inflammatory bowel disease, immunodeficiency, chemotherapy, chronic kidney disease, gastrointestinal surgical procedures, or use of a feeding tube. Toxigenic *C.difficile* bacteria produce both toxin A and toxin B or just toxin B. These toxins disrupt epithelial integrity, stimulate release of inflammatory mediators, and result in pseduomembrane formation.[11] Type 027 is a *C.difficile* strain that produces more types of toxins than other types of *C.difficile*; resulting in more severe CDI and possibly higher mortality rates.[12]

The diagnosis of CDI is based on clinical history and laboratory findings of *C.difficile* toxins in the stool. Symptoms include presence of diarrhea (defined as ≥ 3 unformed stools in 24 hours), cramps, fever, or lower abdominal pain. Laboratory testing cannot distinguish between colonization and infection. The gold standard for CDI diagnosis is lab verification of toxigenic *C.difficile* in stool along with histopathology showing psuedomembranes in patients with clinical symptoms.[11] Symptoms of CDI can range in severity from mild diarrhea to toxic megacolon, fulminant colitis, colonic perforation, multi-organ failure and death.[13] Treatment goals include resolution of diarrhea and reduction of CDI recurrence. Severe CDI may be accompanied by leukocytosis with a white blood cell count (WBC) greater than 15,000 cells/µL and elevated serum creatinine 1.5 times the patients' baseline value secondary to dehydration from extensive diarrhea. Some of the literature uses a Zar score to stratify patients with CDI into mild or severe groups. In the Zar severity scoring, one point each is assigned for age greater than 60 years, temperature greater then 38.3°C, albumin level less than 2.5 mg/dl or WBC greater than 15,000 cells/µl.[14] Patients that score greater than or equal to 2 points are considered to have severe CDI.[14] Severe, complicated CDI can result in shock, hypotension, ileus or megacolon. Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.[15]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 2** which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Agency for Healthcare Research and Quality

In 2016 AHRQ published an updated systematic review on the early diagnosis, prevention, and treatment of CDI, which reviewed data from 2010 through April 2015.[1] Updated antibiotic comparative evidence comes from a RCT comparing fidaxomicin to vancomycin, [16] a 3-arm RCT comparing tolevamer (a non-antibiotic, toxin-binding resin not approved in the U.S.) to metronidazole and vancomycin, [17] and a 3-arm prospective cohort study comparing intravenous (IV) metronidazole to oral metronidazole and vancomycin.[18] The data from the prospective observational cohort study were not included in the AHRQ pooled analysis of RCTs. Data from the 2 recent RCTs were combined with studies from the original 2011 AHRQ report to assess the efficacy of each therapeutic intervention. A summary of all trials, findings and strength of evidence from the AHRQ reports to date is outlined in **Table 1**. Tolevamer does not have any antimicrobial activity, and its efficacy in treating CDI was inferior to metronidazole and vancomycin.[1] Therefore, it was excluded from the pooled data. The finding that vancomycin is more effective than metronidazole for initial cure of CDI in adults was new to the 2016 update.[1] New evidence for the superior effectiveness of fidaxomicin over vancomycin for the prevention of recurrent CDI was also included in the update.[1] No new evidence supports the use of nitazoxanide or rifaximin in preventing recurrent CDI.[1]

Table 1: Summary of standard treatment findings using pooled RCT data from original 2011 AHRQ report and 2016 update[1]

Intervention	Study Information	Findings	Strength of Evidence
Vancomycin vs. metronidazole	4 RCTs N=872	Initial Cure: favors vancomycin over metronidazole (83.9% vs. 75.7%) RR 1.08, 95% CI 1.02 to 1.15	High
	N=705	Recurrent CDI: not significantly different (16.5% vs. 18.7%) RR 0.89, 95% CI 0.65 to 1.23	Moderate
Fidaxomicin vs. vancomycin	2 RCTs N=1,111	Initial Cure: not significantly different (87.6% vs. 85.6%) RR 1.02, 95% CI 0.98 to 1.07	Moderate
	N=962	Recurrent CDI: favors fidaxomicin over vancomycin (14.1% vs. 26.1%) RR 0.55, 95% CI 0.42 to 0.71	High
Abbreviations: CDI = *Clostridium difficile* infection; CI = confidence interval; RCT = randomized controlled trial; RR = relative risk			

Cochrane Collaboration

A 2017 Cochrane systematic review evaluated evidence through January 2017 that studied antibiotic treatment for CDI in adults.[2] Twenty-two studies including 3215 subjects were included in the review. Most of the studies evaluated patients with mild to moderate CDI taking oral antibiotics 4 weeks after completion of therapy. Sixteen studies excluded patients with severe CDI and the other 6 studies had relatively few patients with severe CDI. Twelve different antibiotics were studied: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, cadazolid, LFF517, surtomycin and fidaxomicin. The studies that evaluated metronidazole, vancomycin and fidaxomicin were of moderate quality.[2] For the other nine antibiotics, the evidence was rated as having a high risk of bias due to small study size and substantial patient drop-out before study completion.[2] Four trials provided moderate quality evidence to support vancomycin superiority over metronidazole for achieving resolution of mild to moderate CDI with no relapse.[2] In the pooled analysis, 72% (318/444) of metronidazole patients achieved symptomatic cure compared to 79% (339/428) of vancomycin patients (RR 0.90, 95% CI 0.84 to 0.97).[2] Two large studies of moderate quality found fidaxomicin superior to vancomycin in resolving symptoms of CDI.[2] In the pooled analysis, 71% (407/572) of fidaxomicin patients achieved symptomatic cure compared to 61% (361/592) of vancomycin patients (RR 1.17, 95% CI 1.07 to 1.27).[2] The differences in effectiveness between these antibiotics

were not too large and the advantage of metronidazole is its far lower cost compared to the other two antibiotics.[2] There were no head-to-head trials of fidaxomicin and metronidazole. No firm conclusions can be drawn regarding the efficacy of antibiotic treatment in severe CDI as most studies excluded patients with severe disease.[2]

New Guidelines:

Infectious Disease Society of America/Society for Healthcare Epidemiology of America

Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) 2017 guideline updates were published February 2018.[3] The literature search for the updated guidelines was conducted from 2009 through 2016 for evidence in adult and pediatric patients.[2] The time frame for the literature search did not include bezlotoxumab evidence, therefore bezlotoxumab was not included in the updated guidelines. The most recent treatment guidelines recommend using oral vancomycin or fidaxomicin for an initial CDI episode.[3] Oral fidaxomicin has been associated with a lower recurrence rate than oral vancomycin but is more costly.[3] Metronidazole is no longer recommended as a first line agent, except in circumstances where access to vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.[3] Non-severe CDI is characterized by a white blood cell count (WBC) less than or equal to 15,000 and serum creatinine less than 1.5 mg/dl.[3] In severe CDI, WBC greater than or equal to 15,000 and serum creatinine greater than 1.5 mg/dl are observed.[3] The initial treatment recommendations for CDI are based on the same evidence evaluated by recent systematic reviews compiled by AHRQ and the Cochrane Collaboration. Severe, complicated CDI is now referred to a fulminant CDI in the IDSA/SHEA guidelines.[3] Higher doses of oral vancomycin are recommended for patients with fulminant CDI symptoms, which has not changed from the original 2010 IDSA/SHEA guidance. If ileus is present, rectal vancomycin and intravenous metronidazole are recommended to achieve significant levels in the inflamed gastrointestinal tract.[3] The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode.[3] If vancomycin was used for the first CDI episode, modifying the subsequent vancomycin dose to a tapered and pulsed regimen for recurrent CDI is another strategy to manage recurrent CDI.[3] Metronidazole is not recommended for treatment of recurrent CDI.[3] Patients who have failed to resolve recurrent CDI despite repeated antibiotic treatments may be candidates for fecal microbiota transplantation (FMT).[3] **Table 2** summarizes recommended IDSA/SHEA treatments for various presentations of CDI in adults.

Robust data assessing the optimal approach for treating CDI in children are limited.[3] Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.[3] For second CDI recurrences, vancomycin is recommended over metronidazole in pediatric patients.[3] Fidaxomicin is not FDA approved for use in children less than 18 years of age, so it is not included in the IDSA/SHEA pediatric recommendations.[3] **Table 3** summarizes treatment recommendations for CDI in children.

Table 2. IDSA/SHEA Recommendations for the Treatment of *Clostridium difficile* Infection in Adults[3]

Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Vancomycin 125 mg given 4 times daily for 10 days, OR	Strong/High
	• Fidaxomicin 200 mg given twice daily for 10 days	Strong/High

Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
	• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days[a]	Weak/High
Initial episode, severe[b]	• Vancomycin 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
	• Fidaxomicin 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	• Vancomycin 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Strong/Moderate (oral vancomycin); Weak/Low (rectal vancomycin); Strong/Moderate (intravenous metronidazole)
First recurrence	• Vancomycin 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
	• Use a prolonged tapered and pulsed vancomycin regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
	• Fidaxomicin 200 mg given twice daily for 10 days if vancomycin was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen, OR	Weak/Low
	• Fidaxomicin 200 mg given twice daily for 10 days, OR	Weak/Low
	• Fecal microbiota transplantation[c]	Strong/Moderate

a. All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.
b. The criteria proposed for defining severe or fulminant CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

c. The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Table 3. IDSA/SHEA Recommendations for the Treatment of *Clostridium difficile* Infection in Children

Clinical Definition	Recommended Treatment	Pediatric Dose	Maximum Dose	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low Weak/Low
Initial episode, severe/ fulminant	• Vancomycin × 10 days (PO or PR) with or without metronidazole × 10 days (IV)[a]	• 10 mg/kg/dose qid • 10 mg/kg/dose tid	• 500 mg qid • 500 mg tid	Strong/Moderate Weak/Low
First recurrence, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen[b], OR • Fecal microbiota transplantation	• 10 mg/kg/dose qid • Vancomycin: 10 mg/kg/dose qid;	• 125 mg qid • Vancomycin: 500 mg qid	Weak/Low Weak/Very low

Abbreviations: IV, intravenous; PO, oral; PR, rectal; qid, 4 times daily; tid, 3 times daily.

a.In cases of severe or fulminant CDI associated with critical illness, consider addition of intravenous metronidazole to oral vancomycin.
b. Tapered and pulsed regimen: vancomycin 10 mg/kg with max of 125 mg 4 times per day for 10–14 days, then 10 mg/kg with max of 125 mg 2 times per day for a week, then 10 mg/kg with max of 125 mg once per day for a week, and then 10 mg/kg with max of 125 mg every 2 or 3 days for 2–8 weeks.

National Institute for Health and Care Excellence

National Institute for Health and Care Excellence (NICE) prepared an evidence summary of bezlotoxumab for preventing recurrent CDI.[12] The report provides an analysis of the Phase 3 trials (MODIFY I and MODIFY II) which evaluated the safety and efficacy of bezlotoxumab in preventing recurrence of CDI in patients taking standard-of-care antibiotics. NICE guidance for utilization of bezlotoxumab is expected to be published late May of 2018.

New Formulations:
None identified.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 72 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Bezlotoxumab Infusion

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Bezlotoxumab is a human monoclonal immunoglobulin antibody that binds to and neutralizes *C. difficile* toxin B. Bezlotoxumab received Food and Drug Administration (FDA) approval in October 2016 for reduction of CDI recurrence in conjunction with antibacterial treatment in adults at high risk for CDI recurrence.[5] Bezlotoxumab does not have antibacterial properties and is not indicated as monotherapy for CDI treatment; therefore bezlotoxumab should only be used in combination with antibiotic therapy proven to treat CDI. The recommended dose is a single dose of 10mg/kg administered as an intravenous infusion over 60 minutes during antibacterial treatment for CDI.[5] A trial evaluating the safety and efficacy of bezlotoxumab in children with CDI (MODIFY III) is currently recruiting patients.[19]

Two multi-centered, phase 3, double-blind studies (MODIFY I and II) were conducted to evaluate the safety and efficacy of bezlotoxumab in patients receiving standard-of-care antibiotics for primary or recurrent CDI.[4] Bezlotoxumab either alone or in combination with actoxumab (a human monoclonal antibody that neutralizes *C difficile* toxin A), was compared to placebo to assess the primary efficacy endpoint of rate of recurrent CDI during the 12 weeks after infusion of the study drug.[4] Actoxumab was included in the MODIFY trials to meet FDA recommendations that evaluations of therapies neutralizing toxin A and toxin B be studied separately. Standard-of-care antibiotics included vancomycin, metronidazole or fidaxomicin. The study drug was administered at some point during the 10 to 14 day course of standard-of-care antibiotics at the discretion of the health care provider. The studies were conducted in both hospital and outpatient settings. Enrolled patients were 18 years of age or older and had a confirmed diagnosis of CDI, which was defined as 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.[4]

In the MODIFY I study, patients were randomized 1:1:1:1 to receive a single, one-time infusion of 10 mg/kg of either bezlotoxumab, actoxumab, the combination of bezlotoxumab and actoxumab, or placebo.[4] CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the presenting CDI episode.[4] Patients were assessed for clinical cure of the presenting CDI episode, defined as no diarrhea for 2 consecutive days, following the completion of a 14 day antibiotic regimen.[4] Patients who achieved clinical cure were then assessed for recurrence of CDI through 12 weeks following administration of the study drug.[4] A secondary endpoint, sustained clinical response, was defined as clinical cure of the

presenting CDI episode and no CDI recurrence through 12 weeks after infusion.[4] MODIFY II had similar inclusion and exclusion criteria and similar definitions of clinical endpoints as the MODIFY I trial.[4]

The interim analysis of the MODIFY I trial showed the rate of recurrent infection was significantly higher in the actoxumab group than in the actoxumab–bezlotoxumab group (p=0.02), and more deaths and serious adverse events were found to have occurred in the actoxumab group than in the placebo group.[4] Actoxumab was not efficacious when given alone, so enrollment in the actoxumab monotherapy group was stopped. In the MODIFY II study, the monotherapy actoxumab arm was excluded and patients receiving standard antibiotics for CDI were randomized 1:1:1 to receive a single, one-time, 10 mg/kg infusion of either bezlotoxumab, bezlotoxumab and actoxumab, or placebo.[4]

In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17.4% vs. 27.6%; 95% CI, 15.9 to 4.3; p =0.0003; Absolute Risk Reduction (ARR) 10; NNT 10 and MODIFY II: 15.7% vs. 25.7%; 95% CI 15.5 to 4.3; p = 0.0003, ARR 10; NNT 10).[4] For the secondary endpoint, sustained clinical cure, there was a statistically significant difference between bezlotoxumab and placebo in MODIFY II (66.8% vs. 52.1%; 95% CI 7.7 to 21.4; p <0.0001) but not in MODIFY I (60.1% vs. 55.2%; 95% CI -2.1 to 11.7; p=0.17).[4] However, in the pooled dataset from both trials, the sustained clinical cure rate observed with bezlotoxumab was 63.5% compared to 53.7% with placebo (95% CI 4.8 to 14.5; p=0.0001).[4]

Limitations:
In the MODIFY trials, a similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) while 4% of the patients received oral fidaxomicin as the standard-of-care antibiotic.[4] Because only 4% of participants were taking fidaxomicin in the trials, so it is unclear what benefits bezlotoxumab has in patients who received fidaxomicin. Although it is not specifically licensed for this indication, there is some evidence that fidaxomicin reduces recurrence of CDI compared with vancomycin, and it is not known whether bezlotoxumab offers any benefits over fidaxomicin alone.[12] The duration of benefit of bezlotoxumab beyond a 12 week follow-up is unknown. In addition, the optimal timing of bezlotoxumab administration in conjunction with standard-of-care antibiotics is not clear since bezlotoxumab was administered at variable times based on provider discretion.

Which patient populations are likely to derive the greatest benefit from bezlotoxumab administration is not clear as it was administered to patients with first and recurrent episodes of CDI. Many participants in the trials did not have severe CDI or risk factors for developing severe or recurrent infection. For example, about 65% did not have a previous history of CDI, about 70% of participants were aged less than 75 years, and about 80% of the participants had a Zar score below 2, indicating less severe infection.[12] Low numbers of participants with immunosuppression, elevated temperature or white blood cell count, impaired renal or hepatic function or other serious conditions, (such as pseudomembranous colitis or toxic megacolon) were included in the phase 3 trials.[12]

The FDA noted a number of significant challenges in interpreting the data from the two MODIFY trials. The pre-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence during the 12-week follow-up period after infusion of study drug.[20] The FDA had raised concerns about the CDI recurrence endpoint prior to the commencement of the second trial while the first trial was still ongoing.[20] The concern with the CDI recurrence endpoint is that it ignores the potential impact of the investigational drug on initial clinical cure and counts patients who do not have initial clinical cure of their presenting CDI episode as successes (i.e. not having a recurrence).[20] The FDA had noted that if an imbalance in the initial cure rates is seen, the effect of the study drug on recurrence can be very difficult to interpret.[20] The Agency recommended that the manufacturer use a primary endpoint of global cure (sustained clinical response) defined as clinical cure of the initial CDI episode and absence of CDI recurrence.[20] However, the manufacturer did not modify the trial design after receiving FDA guidance.

In both Phase 3 trials, recurrence rates in the 12-week follow up period were lower in patients who received bezlotoxumab compared to those who received placebo.[20] However, the imbalance in initial cure rates, especially the lower cure rates seen in the bezlotoxumab arm in MODIFY I, make it difficult to interpret the efficacy of bezlotoxumab using recurrence rate as the primary endpoint.[20] Global cure or sustained clinical response is a valid measure of the efficacy of bezlotoxumab and is the more interpretable endpoint because it considers both initial cure of the CDI episode and absence of recurrence.[20] To be a success, a patient needs to achieve clinical cure of the CDI episode and not have a recurrence. While in both trials, there was favorable treatment effect with bezlotoxumab for the pre-specified primary endpoint of reducing recurrences, in both trials there was an imbalance in the initial cure rate (one in favor of bezlotoxumab, the other against bezlotoxumab).[20] While sustained clinical response was not the manufacturer's pre-specified primary endpoint, in the setting of an imbalance in the initial cure rate, the recurrence endpoint is difficult to interpret making it reasonable to evaluate the trials using sustained clinical response as the primary endpoint.[20]

Clinical Safety:

The most common adverse reactions occurring with bezlotoxumab within 4 weeks of infusion with a frequency greater than 4% are outlined in **Table 4**. In patients with a history of CHF, 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 exacerbation during the 12-week study period.[5] Additionally, in patients with a history of CHF, there were more deaths in bezlotoxumab-treated patients (19.5%) than in placebo-treated patients (12.5%).[5] The causes of death varied, and included cardiac failure, infections, and respiratory failure.

Table 4. Adverse Reactions Reported with Bezlotxoumab[5]

Adverse Reaction	Bezlotoxumab (n = 786)	Placebo (N=781)
Nausea	7%	5%
Pyrexia	5%	3%
Headache	4%	3%
Infusion Related Reactions	10%	8%

Table 5 summarizes the pharmacology and pharmacokinetic properties of bezlotoxumab. **Table 6** summarizes the characteristics of the MODIFY I and II trials.

Table 5. Pharmacology and Pharmacokinetic Properties

Parameter	
Mechanism of Action	Human monoclonal antibody that binds to *C.difficile* toxin B and neutralizes its effects
Distribution and Protein Binding	Volume of distribution: 7.33 liters
Elimination	N/A
Half-Life	19 days
Metabolism	Protein Catabolism

Abbreviations: NA = not applicable

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Recurrent CDI in subpopulations at risk for recurrence (age > 65 yo, Prior CDI within past 6 months, immunocompromised)
2) Proportion of patients with global cure
3) Proportion of patients with initial clinical cure
4) Serious adverse events
5) Discontinuations due to adverse events

Primary Study Endpoint:

1) Proportion of patients with recurrent CDI at 12 weeks

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Wilcox MH, et al.[21] DB, PC, MC, RCT 2 Phase 3 trials [MODIFY I (n = 1452; 158 sites in 19 countries) and MODIFY II (n= 1203; 171 sites in 17 countries)]	1. Actoxumab + Bezlotoxumab x1 dose (10 mg/kg each) 2. Actoxumab x1 dose (10 mg/kg) 3. Bezlotoxumab x1 dose (10 mg/kg) 4. Placebo	Demographics: -Median age: 65 y -White: 86% -Inpatient: 68% -Female: 56% -Age ≥65 y: 53% - ≥1 CDI episode in past 6 mos: 28% - ≥2 previous CDIs: 14% -Antibiotics: Metronidazole: 49% Vancomycin: 47% Fidaxomicin: 4% Key Inclusion Criteria: -Adults ≥ 18 years with CDI receiving SOC therapy. (CDI defined as ≥ 3 unformed stools in 24 hours with positive stool test for toxigenic *C.difficile*.)	ITT: 1.773 2.232 3.781 4.773 Attrition: 1.114 (15%) 2.34 (15%) 3.111 (14%) 4.126 (16%)	Primary Endpoint: Proportion of patients with recurrent CDI at 12 weeks MODIFY I: Bezlotoxumab: 17.4% (67/386) Placebo: 27.6% (109/395) Adjusted Difference: 10.1% (95% CI, 15.9 to 4.3; p=0.0003) MODIFY II: Bezlotoxumab: 15.7% (62/395) Placebo: 25.7% (97/378) Adjusted Difference: 9.9% (95% CI, 15.5 to 4.2; p=0.0003) Secondary Endpoints: Sustained cure: initial CDI cure and no CDI recurrence through week 12 MODIFY I 3.60.1% (232/386) 4.55.2% (218/395) Adjusted Difference: 4.8% (95% CI, -2.1 to 11.7; p=0.1722) MODIFY II 3.66.8% (264/395) 4. 52.1% (197/378) Adjusted Difference: 14.6% (95% CI, 7.7 to 21.4; p=0.0001)	10.1 /10 9.9 /10 NS 14.6/ 7	AE (4 weeks after infusion) 1.59% 2.67% 3.62% 4.61% SEA: 1.16% 2.28% 3.20% 4.21% Death: 1.4% 2.6.0% 3.4% 4.4% Nausea: 1. 6% 2. 12% 3. 6% 4. 5% Infusion Site Reactions: 1. 8% 2. 11% 3. 10% 4. 8%	NA NA NA NA NA	**Study: Moderate Quality** **Risk of Bias (low/high/unclear)**: Selection Bias: **Unclear**. Randomized 1:1:1:1 after stratification into 2 groups based on SOC therapy and hospitalization status (inpatient vs. outpatient). Details of randomization process not included in protocol. Performance Bias**: Low**. Unblinded pharmacist prepared the infusion, but not involved in patient assessment. All other investigators were blinded. SOC therapy determined by prescribing physician. Detection Bias: **Low**. Data assessors were blinded. Data from 2 trials pooled to enhance statistical assessment. Attrition Bias: **Low**. Attrition rates were similar across all 4 arms. Analysis completed in ITT population. Reporting Bias: **Low**. All authors reviewed and edited manuscript. Funded by Merck. **Applicability**: Patient: Primarily used in an inpatient setting in older patients – no differentiation between initial or recurrent CDI patients. Intervention: Bezlotoxumab studied as a one-time 10 mg/kg dose only. Actoxumab arm stopped early due to interim analysis showing no benefit and possible harm. No information available about re-dosing

		Key Exclusion Criteria: -UC or Crohn's Disease -Receipt of cholestyramine, rifaximin, or nitazoxanide within 14 days prior to study dose or during the 12 week study		(Pooled data Modify I and II) 3. 63.5% 4. 53.7% Adjusted difference 9.7% (95% CI, 4.8 to 14.5%; p=0.0001)	9.7/ 11	Headache: 1. 4% 2. 6% 3. 5% 4. 3%	NA	bezlotoxumab –only studied as a one-time infusion in conjunction with antibiotic therapy. Comparator: Placebo appropriate as no other therapies are approved to prevent CDI recurrence in combination with SOC. Outcomes: Global cure would have been a better primary endpoint. Longer follow-up needed to determine durability of bezlotoxumab or if re-dosing is needed. Setting: 322 sites in 30 countries with 60% of sites represented outside of U.S.

Abbreviations: AE = Adverse effect; CDI = *Clostridium difficile* infection; CI = confidence interval; DB = double blind; ITT = intention to treat; MC = multi center; Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; RCT = randomized controlled trial; SAE = serious adverse effect; SOC = standard of care (metronidazole, vancomycin, or fidaxomicin); UC = ulcerative colitis; Y = Years

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAVEN	VIAL	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	VANCOCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	VANCOMYCIN HCL	VANCOMYCIN HCL	Y
ORAL	CAPSULE	FLAGYL	METRONIDAZOLE	Y
ORAL	CAPSULE	METRONIDAZOLE	METRONIDAZOLE	Y
ORAL	TABLET	FLAGYL	METRONIDAZOLE	Y
ORAL	TABLET	METRONIDAZOLE	METRONIDAZOLE	Y
ORAL	TABLET ER	FLAGYL ER	METRONIDAZOLE	Y
ORAL	TABLET	DIFICID	FIDAXOMICIN	N
IV	VIAL	ZINPLAVA	BEZLOTOXUMAB	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 3 2017

1 exp Clostridium difficile/	*11358*
2 vancomycin.mp. Or exp Vancomycin/	*23770*
3 metronidazole.mp. or exp Metronidazole/	*16817*
4 fidaxomicin.mp.	*249*
5 bezlotoxumab	*30*
6 2 or 3 or 4 or 5	*39462*
7 1 and 6	*2010*
8 limit 7 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase IV or comparative study or controlled clinical trial or meta-analysis or practice Guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews	*357*
9 limit 8 to English language and humans and yrs. =2015-current	*72*

Appendix 3. Highlights of Prescribing Information

ZINPLAVA- bezlotoxumab injection, solution
Merck Sharp & Dohme Corp.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZINPLAVA safely and effectively. See full prescribing information for ZINPLAVA.

ZINPLAVA™ (bezlotoxumab) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

ZINPLAVA is a human monoclonal antibody that binds to Clostridium difficile toxin B, 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. (1)

Limitation 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. (1)

DOSAGE AND ADMINISTRATION

- Administer ZINPLAVA during antibacterial drug treatment for CDI. (2.1)
- The recommended dose is a single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes. (2.2)
- Dilute prior to intravenous infusion. Administer via a low-protein binding 0.2 micron to 5 micron in-line or add-on filter. See Full Prescribing Information for dilution and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 1,000 mg/40 mL (25 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Heart Failure: Was reported more commonly in ZINPLAVA-treated patients with a history of congestive heart failure (CHF) in the two Phase 3 clinical trials. In patients with a history of CHF, ZINPLAVA should be reserved for use when the benefit outweighs the risk. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (reported in ≥4% of patients) included nausea, pyrexia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2016

Appendix 4: Prior Authorization Criteria

Fidaxomicin (Dificid®)

Goal(s):

- To optimize appropriate treatment of *Clostridium difficile*-associated infection.

Length of Authorization:

10 days

Requires PA:

- Fidaxomicin

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of *Clostridium difficile*-associated infection (CDI)?	**Yes:** Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have at least one documented trial of or contraindication to appropriate therapy with vancomycin?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have severe, complicated CDI (life-threatening or fulminant infection or toxic megacolon)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 10 days

P&T / DUR Review: *5/18 (DM); 5/15 (AG); 4/12*
Implementation: *6/18/18; 10/15; 7/12*

Bezlotoxumab (Zinplava™)

Goal(s):

- To optimize appropriate prevention of recurrent *Clostridium difficile*-associated infection.

Length of Authorization:

- One time infusion

Requires PA:

- Bezlotoxumab (physician administered and pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of **recurrent** *Clostridium difficile*-associated infection (CDI)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient currently receiving vancomycin or fidaxomicin?	**Yes**: Approve for one dose	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *5/18(DM)*
Implementation: *6/18/18*