

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761046Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761046
PDUFA Goal Date	July 23, 2016
OSE RCM #	2016-104 & 2016-20
Reviewer Name(s)	Mona Patel, Pharm.D., Senior Risk Management Analyst
DRISK Team Leader	Naomi Redd, Pharm. D., Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	April 27, 2016
Subject	Evaluation to determine if a REMS is necessary
Established Name	bezlotoxumab
(Proposed) Trade Name	Zinplava
Applicant	Merck Sharp & Dohme Corporation
Therapeutic Class	human monoclonal antibody (mAb) directed to the C-terminus receptor-binding region of the C. difficile toxin B
Formulation(s)	Oral tablet
Dosing Regimen	10 mg/kg administered as an IV infusion over 60 minutes as a single dose
Proposed Indication(s)	Prevention of Clostridium difficile infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI

Table of Contents

EXECUTIVE SUMMARY	3
1 Introduction	3
2 Background	3
2.1 Product Information	3-4
2.2 Regulatory History	4
3 Therapeutic Context and Treatment Options	4
3.1 Description of the Medical Condition ¹	4-5
3.2 Description of Current Treatment Options	5-6
4 Benefit Assessment.....	6-7
5 Risk Assessment & Safe Use Conditions.....	7-8
6 Expected Postmarket Use.....	8
7 Evaluating the Need for a REMS.....	8
8 Risk Management Activities Proposed by the Applicant.....	8
9 Conclusion & Recommendations	9
10 Appendices	9

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zinplava (bezlotoxumab) is necessary to ensure the benefit of this product outweighs its risk. Merck Sharp & Dohme Corporation submitted a Biologics License Application (BLA) 761046 for Zinplava (bezlotoxumab) for the prevention of Clostridium difficile infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. According to the applicant, there are minimal risks associated with the use of bezlotoxumab. The applicant did not submit a REMS with this application but submitted a Patient Information Sheet and a proposed Risk Management Plan.

Based on the information available at the time of this review, DRISK is not recommending a REMS. The risks seen with this drug will be communicated through labeling.

1 Introduction

Merck Sharp & Dohme Corporation submitted a Biologics License Application (BLA 761046) for Zinplava (bezlotoxumab) with the proposed indication for the prevention of Clostridium difficile infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. This application is under review in the Division of Anti-Infective Products. The applicant did not submit a REMS with this application but proposed an enhanced pharmacovigilance plan for the drug.

2 Background

2.1 PRODUCT INFORMATION

Zinplava (bezlotoxumab) is a new molecular entity, human monoclonal antibody (mAb), directed to the C-terminus receptor-binding region of the C. difficile toxin B molecule. Bezlotoxumab is of the G1 subclass [REDACTED] (b) (4).¹ Merck Sharp & Dohme Corporation proposed for bezlotoxumab to be indicated to prevent Clostridium difficile infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. The proposed dosing schedule is 10 mg/kg as an intravenous infusion over 60 minutes as a single dose to be administered during a course of antibiotic therapy for CDI. The dosage formulation is 1000 mg/40 mL (25 mg/mL) solution in a single-dose vial.

This is a NME 505 (b)(1) application that is under priority review with a Prescription Drug User Fee Act date of July 22, 2016. The determination for the efficacy of the product is based upon two randomized, double-blind, placebo-controlled, multicenter, Phase 3 studies (MODIFY I and MODIFY II). Bezlotoxumab is not licensed in the United States nor anywhere in the world.

¹ Clinical Overview (section 2.5), bezlotoxumab

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208573 relevant to this review:

- 12/30/2005: IND 12823 active
- 5/12/2010: Fast Track designation granted for CDI
- 9/29/15: Pre-BLA Meeting
- 11/23/2015: BLA Received
- 2/23/2016: Midcycle Meeting
- 3/22/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for bezlotozumab

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

According to the U.S. Centers for Disease Control, in 2011, *C. difficile* was responsible for approximately 453,000 infections and was associated with approximately 29,000 deaths.² Based on data from the U.S. National Hospital Discharge Survey, the incidence of reported CDI in acute-care hospitals nearly tripled between 1996 and 2005, from 31 to 84 per 100,000 population between 1996 and 2005.³ Similarly, according to the U.S. Nationwide Inpatient Sample, a 3-fold increase was recorded between 1993 and 2008 (from 2.61 to 8.75 cases per 1,000 discharges); the rate began to plateau in 2009 (8.53 cases per 1,000 discharges).⁴ A recent report from the United States indicated that community-associated CDI was more common in women than men (adjusted incidence per 100,000 among women 61 versus men 42.5 and also recurred more frequently in women than men (adjusted incidence per 100,000 among women 8.8 versus men 5.2).⁵

One of the greatest challenges in managing CDI is preventing its recurrence. After initial treatment and resolution of diarrhea, 15% to 35% of CDI patients will experience recurrence.⁶ Concurrent with the

² Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015 Feb 26;372(9):825-34.

³ Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353(23):2442-9.

⁴ Lessa FC, Gould CV, McDonald LC. A current status of *clostridium difficile* infection epidemiology. *Clin Infect Dis* 2012;55(S2):S65-S70.

⁵ Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015 Feb 26;372(9):825-34.

increasing incidence in CDI, the incidence of life-threatening CDI complications has also been increasing in recent years. Reported mortality rates from CDI in the United States increased from 5.7 to 23.7 per million population between 1999 and 2004.⁷

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Metronidazole, vancomycin, and fidaxomicin are recommended in the treatment of CDI. However, only vancomycin and fidaxomicin are FDA approved to treat CDI. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI whereas vancomycin or fidaxomicin are the drugs of choice for an initial episode of severe CDI.

Vancocin (vancomycin) is an antibacterial drug approved by the FDA in 1986 for the treatment of CDI. Dificid (fidaxomicin), approved in 2011, is a macrolide to treat CDI. Neither of these drugs contains a Boxed Warning.

The table below summarizes these treatment options:

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic),	Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management
Flagyl (metronidazole) ⁸	1963	trichomoniasis, amebiasis, anaerobic infections	C-diff: 500 mg orally three times daily for 10 ^(b) ₍₄₎ days	<i>Carcinogenic in mice & rats</i> Hepatic, Renal, Fungal, Blood dyscrasias, Drug-Resistant Bacteria & Parasites	<i>Boxed Warning</i>
Vancocin (vancomycin) ⁹	1986	C diff, enterocolitis	125 mg orally four times daily for 10 days	Nephrotoxicity, ototoxicity	None
(Dificid) (fidaxomicin) ¹⁰	2011	C.diff	200 mg orally twice daily for 10 days	Hypersensitivity Rxns	None

A colectomy should be considered for severely ill patients.¹¹Other therapies that have been used are fecal microbiota for transplantation. CDI is the most commonly recognized cause of diarrhea-associated

⁶ Bouza E. Consequences of Clostridium difficile infection: understanding the healthcare burden. Clin Microbiol Infect. 2012 Dec;18 Suppl 6:5-12.

⁷ Redelings MD, Sorvillo F, Mascola L. Increase in Clostridium difficile-related mortality rates, United States, 1999-2004. Emerg Infect Dis 2007;13(9):1417-9.

⁸ Flagyl (metronidazole) US Prescribing Information 7/2015

⁹ Vancocin (vancomycin) US Prescribing Information 12/2011

¹⁰ Dificid (fidaxomicin) US Prescribing Information 2/2015

nosocomial infection in adults in the United States and Europe. Currently there are no approved preventative treatments of CDI recurrence, thereby making availability of safe and efficacious therapies for prevention of CDI recurrence a critical unmet medical need.

4 Benefit Assessment

The evidence of clinical benefit for bezlotoxumab in preventing CDI recurrence in patients 18 years or older receiving antibiotic therapy for CDI is derived from two pivotal Phase 3 studies. MODIFY I is a randomized, double-blind, placebo controlled, adaptive design, single dose trial to determine if actoxumab, bezlotoxumab, and/or actoxumab+bezlotoxumab reduced the proportion of patients with recurrence of CDI through 12 weeks following administration of the study infusion. Actoxumab is an investigational human monoclonal antibody which binds to C. difficile toxin A.¹ According to the applicant's submission, 390 patients were treated. The second trial, MODIFY II, was a randomized, double-blind, placebo controlled, single dose trial with the same primary endpoint as MODIFY I. Three hundred ninety six patients were treated in this trial.¹ A secondary endpoint was global cure, defined as clinical cure of CDI episode and no CDI recurrence through 12 weeks after infusion.¹

The Phase 3 clinical development program enrolled patients at over 300 sites in 30 countries.¹

Patients enrolled in these studies had a median age of 65 years. Fifty-seven percent of patients were female and 85% were white.¹² According to the applicant's submission, recurrence rate through 12 weeks was 16.5 versus 26.6 in the placebo arm. Global cure was assessed by the applicant as 64% for bezlotoxumab vs. 54% for placebo.¹

At this time, it has not been determined if the results seen with bezlotoxumab for the prevention of CDI recurrence in patients 18 years or older receiving antibiotic therapy for CDI are clinically meaningful and statistically significant. DAIP raised concerns with the data presented by the applicant to support the efficacy of bezlotoxumab in preventing CDI. MODIFY I results were concerning due to the lower rate of initial cure as well as the failure to achieve significance in global cure for bezlotoxumab compared to placebo. Additionally, MODIFY 2 results appeared to have an imbalance in the number of subjects who had a new episode of diarrhea following clinical cure but whose stool was not collected for toxin testing.

DAIP continues to analyze the differing efficacy results in the two phase 3 trials and an Advisory Committee meeting has been planned for June 9, 2016, to discuss the issues surrounding the results.

5 Risk Assessment & Safe Use Conditions

¹¹ Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, et al. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 2005;26(3):273-80.

¹² Zinplava (bezlotozumab) draft label, April 20, 2016

According to the applicant's submission, the safety of bezlotoxumab at the single dose of 10 mg/kg was evaluated in 1563 patients in the 2 Phase 3 trials.¹ Adverse event data was summarized by system organ classes (SOCs) and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

According to Merck's proposed label, (b) (4)
(b) (4)¹² In the bezlotoxumab arm, 13.49% of patients reported infection and infestation (i.e., sepsis), 6.36% of patients reported gastrointestinal issues (c.diff, diarrhea), 4.71% reported cardiac disease (cardiac failure), and 3.82% of patients reported respiratory issues (i.e., pneumonia).¹³ Four of 786 patients treated with bezlotoxumab had serious adverse reactions that were considered to be drug-related (one report each of diarrhea, ventricular tachyarrhythmia, hematuria, sepsis, and cerebral hemorrhage); all occurred within 4 weeks of receiving bezlotoxumab. Of these four patients, one patient discontinued the bezlotoxumab infusion due to an adverse event (ventricular tachyarrhythmia). There were no other bezlotoxumab treated patients who discontinued therapy due to adverse reactions. Mortality rates were similar across treatment arms (7.1% in bezlotoxumab arm and 7.6% in the placebo treatment arm).¹²

No serious adverse reactions were proposed by the applicant to be included under the Warnings & Precautions section of the label.

At the time of this review, the safety issues had not been discussed by DAIP for inclusion in the label.

6 Expected Postmarket Use

Bezlotoxumab will be administered in inpatient settings such as hospitals and long-term care facilities, and the likely prescribers are gastrointestinal and infectious disease specialists, primary care and emergency-room physicians, and hospitalists who will be familiar with managing any risks, such as infusion reactions.

7 Evaluating the Need for a REMS

CDI is the most commonly recognized cause of diarrhea-associated nosocomial infection in adults in the United States and Europe. Metronidazole, vancomycin, and fidaxomicin are recommended in the treatment of CDI. However, only vancomycin and fidaxomicin are approved by the FDA to treat CDI. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI whereas vancomycin or fidaxomicin are the drugs of choice for an initial episode of severe CDI. Currently there are no approved treatments for the prevention of CDI recurrence. The sponsor's proposed indication for bezlotoxumab is for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. Bezlotoxumab is to be administered as a single dose during a course of antibiotic therapy for CDI.

¹³ February 23, 2016 Midcycle Slides by Drs. Hiwot Hiruy & Shrimant Mishra

The applicant did not propose any safety issues to be listed under the Warnings & Precautions section of the label [REDACTED] (b) (4)

(b) (4) At the time of completion of this review, the Division of Anti-Infective Products had not begun discussion of the safety issues for inclusion under the Warnings & Precautions section of labeling.

The likely prescribing population for bezlotozumab will be practicing gastrointestinal and infectious disease specialists, primary care and emergency-room physicians, and hospitalists.

8 Risk Management Activities Proposed by the Applicant

Merck Sharp & Dohme Corporation did not propose any risk management activities for bezlotozumab beyond routine pharmacovigilance and labeling. The applicant proposed a Patient Information Sheet to be provided to patients when this drug is dispensed.

9 Conclusion & Recommendations

At the time of this review, evaluation of safety information and labeling was ongoing, therefore based on the data available at the time of this review, anticipated prescribing population, and patient population for use of this drug, DRISK is not recommending a REMS for bezlotozumab. Please notify DRISK if new safety information becomes available; this recommendation can be reevaluated.

10 Appendices

10.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

- Merck Sharp & Dohme Corporation Clinical Overview (section 2.5), bezlotozumab
- February 23, 2016 Midcycle Slides by Drs. Hiwot Hiruy & Shrimant Mishra
- Zinplava (bezlotozumab) draft label, April 20, 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONA G PATEL
04/27/2016

CYNTHIA L LACIVITA
04/27/2016
Concur