CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761046Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 5, 2016
To:	Sumathi Nambiar, MD, MPH Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Puja Shah, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZINPLAVA (bezlotoxumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761046
Applicant:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On November 22, 2015, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted for the Agency's review an Original Biologics Licensing Application (BLA) 761046 for ZINPLAVA (bezlotoxumab) injection. ZINPLAVA is a New Molecular Entity (NME) with a proposed indication for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Anti-Infective Products (DAIP) on January 6, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZINPLAVA (bezlotoxumab) injection.

2 MATERIAL REVIEWED

- Draft ZINPLAVA (bezlotoxumab) injection PPI submitted on November 22, 2015 and received by DMPP and OPDP on September 20, 2016.
- Draft ZINPLAVA (bezlotoxumab) injection Prescribing Information (PI) submitted on November 22, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 21, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KAREN M DOWDY
10/05/2016

PUJA J SHAH
10/05/2016

LASHAWN M GRIFFITHS
10/05/2016

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	761046
Product Name:	Bezlotoxumab
PMC #5 Description:	Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.
PMC Schedule Milestones:	Final Report Submission: 03/31/2017

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☐ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☐ Manufacturing process analysis
   - ☐ Other

The sponsor provided microbial retention data for the (b) (4). The acceptance criteria were met. However, the study design was deficient. The protocol has to be modified and the study should be repeated with a suitable surrogate for bezlotoxumab Drug Product (DP) (b) (4) (b) (4). The sponsor agreed to repeat the microbial retention (b) (4) study (b) (4) (b) (4).

2. Describe the particular review issue and the goal of the study.

(b) (4)

The goal of the study is to perform the filter validation studies, as recommended by the Agency.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☒ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

The Sponsor will repeat the microbial retention (b) (4) study (b) (4) (b) (4). The Sponsor will provide a summary of the revised microbial retention (b) (4) study (b) (4) (b) (4) (b) (4)

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ (signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	761046
Product Name:	Bezlotoxumab
PMC #7 Description:	Perform low endotoxin recovery studies (b) (4) (b) (4) Use an endotoxin standard as the spiking material.
PMC Schedule Milestones:	Final Report Submission: 10/23/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☐ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☐ Manufacturing process analysis
   - ☐ Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

An LER study has not yet been performed (b) (4)

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency

☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☐ Other

Describe the agreed-upon study:

The Sponsor will perform an LER study (b) (4)
(b) (4)
(b) (4) The sponsor will submit the results of this study to the BLA within three months of BLA approval.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ (signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	761046	
Product Name:	Bezlotoxumab	
PMC #6 Description:	Develop a valid *in vitro* endotoxin assay for drug product release testing. Conduct studies to evaluate sample preparation, sample pre-treatment, and alternative test methods for endotoxin detection.	
PMC Schedule Milestones:	Final Report Submission:	07/23/2018

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   - ☐ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☒ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☐ Manufacturing process analysis
   - ☐ Other

(b) (4) (b) (4) The sponsor has committed to develop a valid *in vitro* endotoxin assay for DP release testing within 24 months of product approval. (b) (4) (b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4) (b) (4) The goal of the study is to develop a valid in vitro endotoxin assay for DP release testing.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization

☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☐ Other

Describe the agreed-upon study:

The Sponsor will perform the study to determine the most appropriate *in vitro* endotoxin assay for DP release testing, including evaluation of sample preparation and pre-treatment, as well as alternate methodologies for endotoxin detection. Sponsor will submit the new method (and corresponding validation information) to the BLA within 24 months of the BLA approval.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ (signature line for BLAs only)

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

/s/

JOSEPH C DAVI
09/28/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 22, 2016

To: Christopher Davi, MS
Senior Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Adam George, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 761046 Bezlotoxumab injection, for intravenous use**

This consult review is in response to DAIP's January 6, 2016, request for OPDP's review of the draft package insert (PI) for BLA 761046 Bezlotoxumab injection, for intravenous use (Bezlotoxumab). OPDP's review of the PI is based on the substantially complete version titled "BezlotoxPI.21Sept16clean.docx" sent by email on September 21, 2016 from Christopher Davi to Adam George. We had two comments for section 6.1 Clinical Trials Experience. These comments are incorporated into the PI attached to this consult response for your reference.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ADAM N GEORGE
09/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
BLA# 761046	NDA Supplement #: BLA Supplement #: N/A Original Application	Efficacy Supplement Category: N/A ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (MK-6072) Established/Proper Name: Bezlotoxumab Dosage Form: Injection (intravenous) Strengths: 25 mg/mL		
Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck and Co., Inc. Agent for Applicant (if applicable): N/A		
Date of Application: November 22, 2015 Date of Receipt: November 23, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: July 23, 2016	Action Goal Date (if different): October 23, 2016	
Filing Date: January 22, 2016	Date of Filing Meeting: January 6, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years and older.		
Type of Original NDA: N/A AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	X 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard X Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? N/A	Resubmission after refuse to file? N/A
Part 3 Combination Product? N/A ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

X Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): IND 12,823	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	X	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.				N/A
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	X	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: N/A ☐ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** X Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐	X	

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	X	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	X	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	X	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	X	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	X	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	X	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	X	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	X	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

	X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X	☐		
Is the PI submitted in PLR format?[4]	X	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	X	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	X X	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: **If PI not submitted in PLLR format**, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	☐	☐	Will be done when SCPI is available
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X	☐		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	X	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	X	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	X		DMEPA DRISK OSI
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	X	☐		September 29, 2015
Any Special Protocol Assessments (SPAs)? **Date(s):** See DARRTS ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			December 21, 2012

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 6, 2016

BACKGROUND: Merck has submitted their BLA for the fully human monoclonal antibody (mAb) for CDI. Please see attached PDF file for additional information.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J. Christopher Davi, MS	Y
	CPMS/TL:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Dmitri Iarikov, MD, PhD		
Division Director/Deputy	Sumathi Nambiar, MD, MPH		
Office Director/Deputy	Joseph Toerner, MD, MPH		
Clinical	Reviewer:	Shrimant Mishra, MD Hiwot Hiruy, MD	
	TL:	Dmitri Iarikov, MD, PhD	
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerian Grande, PhD	
	TL:		
Clinical Pharmacology	Reviewer:	He Yang, PhD	Y
	TL:	Seong Jang, PhD	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

APPEARS THIS WAY ON ORIGINAL

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Terry Miller, PhD	
	TL:	Wendelyn Schmidt, PhD	
Statistics (carcinogenicity)	Reviewer:	Cheryl A. Dixon, PhD	
	TL:	Karen Higgins, PhD	
Product Quality (CMC) Review Team:	ATL:	William Hallett, PhD	Y
	RBPM:	Andrew Shiber	Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Not assigned	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Not assigned	
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Not assigned/No REMS required	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Not assigned	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Not assigned	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Not Assigned	
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Not assigned	
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain: N/A	X YES ☐ NO
• Electronic Submission comments **List comments**: Possible issues	☐ Not Applicable X No comments

CLINICAL **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: N/A	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: None at this time ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	X YES Date if known: 6/9/16 ☐ NO ☐ To be determined Reason: Clinical/Statistical/Efficacy
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**: None	X Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**: N/A	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**: None	 ☐ YES ☐ NO X YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**: None	☐ Not Applicable X YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**: None	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**: None	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A X YES ☐ NO X YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	X YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Edward M. Cox, MD, MPH, Office Director, OAP **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): March 22, 2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review X Priority Review
ACTION ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
N/A	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
X	If priority review, notify applicant in writing by day 60 (see CST for choices)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

JOSEPH C DAVI
07/28/2016

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date:	June 3, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products (OBP) Jibril Abdus-samad -S Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.06.03 11:34:01 -04'00'
Through:	William Hallet, PhD, Quality Reviewer Division of Biotechnology Review and Research II William H. Hallett -S Digitally signed by William H. Hallett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001134757, cn=William H. Hallett -S Date: 2016.06.03 11:56:05 -04'00'
Application:	BLA 761046
Product:	Zinplava (bezlotoxumab)
Applicant:	Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc.
Submission Dates:	November 23, 2015; March 14, 24; May 9, 2016

Executive Summary:

The container label and carton labeling for Zinplava (bezlotoxumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 May 1, 2016 to August 1, 2016]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on May 9, 2016 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 761046 Zinplava (bezlotoxumab) on November 23, 2015. Table 1 lists the proposed characteristics of Zinplava (bezlotoxumab). The Applicant submitted a container label and carton labeling on November 23, 2015. Subsequent to recommendations from the Division of Medication Error Prevention and Analysis and an inquiry from OBP, the Applicant submitted updated labeling on March 14 and 24, 2016 respectively. This review evaluates these updated labeling.

Table 1: Proposed Product Characteristics of Zinplava (bezlotoxumab).

Proprietary Name:	Zinplava
Proper Name:	bezlotoxumab
Indication:	Monoclonal antibody (b) (4) Clostridium difficile toxin B indicated for the prevention of Clostridium difficile infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.
Dose:	10 mg/kg based on patient body weight as an intravenous infusion over 60 minutes as a (b) (4) (b) (4) dose
Route of Administration:	Intravenous Infusion
Dosage Form:	Injection
Strength and Container-Closure:	1,000 mg/40 mL in single-dose vials
Storage and Handling:	Store in a refrigerator, 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do Not Freeze. Do Not Shake.

Materials Reviewed:

- Container Label
- Carton Labeling

(b) (4)

[redacted]

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

(2) The name, address, and license number of manufacturer; *conforms*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers; *not applicable*.

(6) The statement: "'Rx only'" for prescription biologicals *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label; *not applicable*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose.

Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *not applicable*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *insufficient data to support*.

> OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).
>
> Applicant's May 9, 2016 response: The length of the label is 110 mm and the outer circumference of the vials is 119.4 mm, thereby providing a gap of 9.4 mm along the full height of the vial for inspection of the vial contents. The bottom of the vial is not covered, also allowing for inspection of the contents. Thus, the label is affixed to the vial in a manner such that "*a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents*," per the requirements of 21 CFR 610.60(e).
> *Applicant's response is acceptable*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

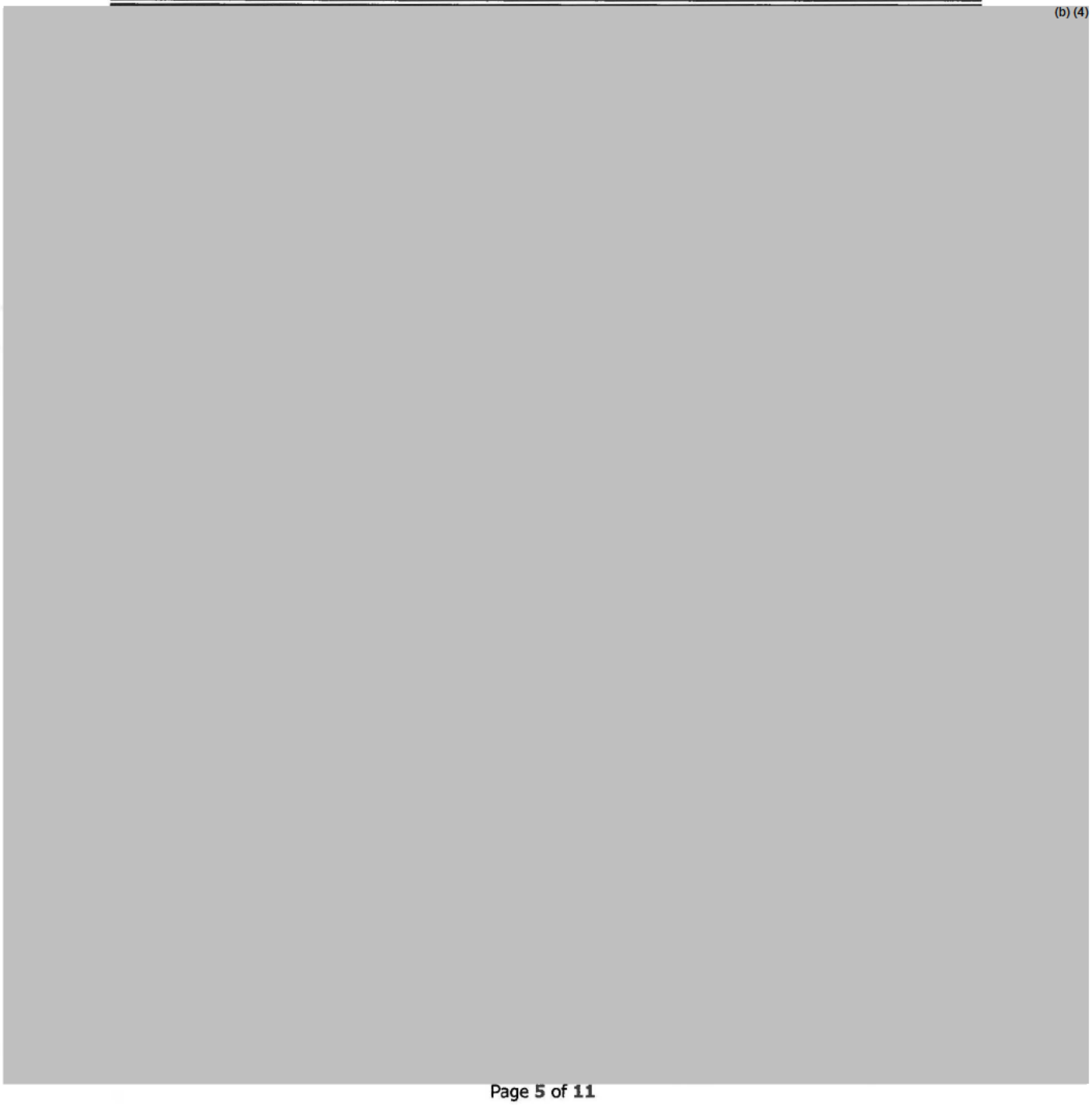
I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

(b) (4)



II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

b) The name, addresses, and license number of manufacturer; *conforms*.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.

f) The number of containers, if more than one; *not applicable*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *does not conform*.

> OBP Request: Add "Do not Freeze" to appear with the storage and handling information. For example, "Do not freeze. Do not shake."
> *Applicant revised as requested.*

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*

o) The adjuvant, if present; *not applicable.*

p) The source of the product when a factor in safe administration; *not applicable.*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable.*

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Zinplava (bezlotoxumab) is a monoclonal antibody.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable.*

D. 21 CFR 610.64 Name and address of distributor: *not applicable.*

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

> Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. However, the list of ingredients requires removal of a trailing zero and revision of the amount of sodium chloride per mL.

> OBP Requests:
> Delete the trailing zeros from the list of ingredients (0.80 mg to 0.8 mg).
> *Applicant revised as requested.*

We think the amount of sodium chloride per mL is (b) (4). Confirm and revise the list of ingredients.

Applicant's May 9, 2016 response: The Sponsor proposes to represent the target sodium chloride concentration in the MK-6072 formulation as 8.77 mg/mL, as determined by the target molar concentration of (b) (4)

(b) (4)

Upon discussion with the OBP Quality reviewer, the Applicant's response is acceptable.

Additional Labeling Concerns

This section describes additional labeling recommendations and concerns provided to the Applicant.

1. Update the container label and carton labeling to reflect the approved proprietary name "Zinplava" for bezlotoxumab.
   Applicant revised as requested.

2. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.
   Applicant confirmed there is no text on the ferrule or cap overseal.

3. Your proposed carton labeling displays (b) (4)

   It is unclear which regulation(s) you are using to display this information on your proposed carton labeling. Please cite the regulation(s) you are using to display this manufacturer information. Your response to this inquiry will inform our forthcoming labeling comments.

   Applicant's March 24, 2016 Response:

   (b) (4)

   (b) (4) Based on FDA feedback for other products, the Sponsor is now reconsidering this practice, and therefore proposes to remove this statement from the MK-6072 carton labeling.
   Applicant's response is acceptable.

Conclusions:

The container label and carton labeling for Zinplava (bezlotoxumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 May 1, 2016 to August 1, 2016]. Labeling deficiencies were identified, and resolved. The container label and carton labeling submitted on May 9, 2016 are acceptable (see below).

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 18, 2016
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	BLA 761046
Product Name and Strength:	Bezlotoxumab injection 1,000 mg/40 ml (25 mg/mL)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck & Co., Inc.
Submission Date:	May 9, 2016
OSE RCM #:	2016-21-1
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anti –Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Zinplava (bezlotoxumab) injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck submitted responses to DMEPA's initial recommendations (*see* Appendix B) and to additional Agency collaborative recommendations with the Office of Biotechnology Product (OBP) Product Quality Reviewer (*see* Appendix C). We found Merck's rationale regarding having different NDC numbers on the container label and carton labeling appropriate (Appendix B). We note that the Merck revised the container label and carton labeling to include the approved proprietary name Zinplava and accepted our remaining recommendations.

3 CONCLUSION

The revised container label and carton labeling for Zinplava (bezlotoxumab) injection are acceptable from a medication error perspective. We defer to the OBP Product Quality Reviewer to determine if Merck's response is acceptable regarding the visual inspection area and the amount of sodium chloride per mL (See Appendix C).

DMEPA has no further recommendations at this time.

[1]Kolejian, S. Label and Labeling Review for Bezlotoxumab for Injection (BLA 761046). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 2. OSE RCM No.: 2016-21.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SEVAN H KOLEJIAN
05/18/2016

BRENDA V BORDERS-HEMPHILL
05/19/2016

Clinical Inspection Summary (CIS)

Date	May 12, 2016
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation (DCCE)
To	J. Christopher Davi, M.S., Senior Regulatory Project Manager Shrimant Mishra, M.D., Medical Officer Dmitri Iarikov, M.D., Ph.D., Medical Team Leader Division of Anti-Infective Products (DAIP)
Application	BLA 761046
Applicant	Merck Sharp and Dohme, Inc.
Drug	Bezlotoxumab (pending, Zinplava®)
New Molecular Entity	Yes
Review Priority	Priority
Proposed Indication	Prevention of *Clostridium difficile* infection recurrence
Consultation Date	January 27, 2016
CIS Goal Date	April 15, 2016
Action Goal Date	July 23, 2016
PDUFA Due Date	July 23, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Merck Sharp & Dohme, Inc. (**Merck**) proposes the use of bezlotoxumab for the prevention of *Clostridium difficile* (**CD**) infection recurrence in adults (age ≥ 18 years) receiving the [redacted] (b) (4) antibiotic therapy for CD infection (**CDI**).

The two pivotal studies (P001 and P002) for this BLA were audited at five good clinical practice (**GCP**) inspections, at the sponsor site and at four clinical investigator (**CI**) sites with high numbers of subjects enrolled, deaths, serious adverse events (**SAEs**), and/or protocol deviations.

A Form FDA 483 was issued at the sponsor site and at two CI sites for minor or limited deficiencies unlikely to be significant to the study outcome. At all four CI sites, overall study conduct appeared GCP-compliant, including study oversight by the sponsor and by the institutional review board (**IRB**). All audited NDA data were adequately verifiable against source records and case report forms (**CRFs**). The data from the four CI sites appear reliable as reported in the BLA.

II. BACKGROUND

Bezlotoxumab is a human IgG_1 kappa monoclonal antibody (**MA**) with high affinity for CD toxin B. The efficacy and safety of bezlotoxumab were evaluated in two pivotal studies with a combined enrollment of 1664 subjects at risk for CDI recurrence (**CDIR**).

Study P001 (MODIFY I)

This randomized, double-blind, placebo-controlled study was conducted at 184 CI sites worldwide. The primary study objective was to determine if a single intravenous (**IV**) infusion of MAs to both CD toxins A and B decreases the incidence of CDIR over 12 weeks, relative to the MA to either CD toxin alone or to placebo.

- In this study, MK 3415A (MAs to both CD toxins A and B) was the primary investigational product (**IP**) of interest. Bezlotoxumab (MK-6072, MA to CD toxin B) served as one of the two active study medications against which the efficacy of MK-3415A was compared (along with MK-3415, MA to CD toxin A).
- A total of 1452 adult subjects (age ≥ 18 years) receiving the standard of care antibiotic treatment for CDI (oral metronidazole, vancomycin, or fidaxomicin) were randomized in equal ratio to four CDI prophylaxis groups:
  - MAs to CD toxins A and B (MK-3415A): IP of interest, N = 403 (28%)
  - MA to CD toxin A (MK-3415): N = 242 (17%)
  - MA to CD toxin B (MK-6072): bezlotoxumab, N = 403 (28%)
  - Placebo (normal saline): N = 404 (28%)
- The primary endpoint was defined as the proportion of subjects with CDIR through Week 12. All active study medications (MAs) were dosed at 10 mg/kg as a single IV infusion over 60 minutes. CDIR was defined as any new diarrhea (following clinical cure of baseline CDI) with stool testing positive for toxigenic CD.
- This study was conducted under an adaptive design in which enrollment into MK-3415 and/or MK-6072 groups could be discontinued if interim analysis showed MK-3415A to be significantly more effective than MK-3415 and/or MK-6072. (MK-3415A showed no advantage over MK-6072.)

Study P002 (MODIFY II)

This study was conducted after completion of Study P001, at 200 CI sites worldwide. The study was similar to Study P001, but with bezlotoxumab as the IP of interest instead of MK-3415A. The primary study objective was to compare bezlotoxumab (MK-6072, MA to CD toxin B) with MK-3415A (MAs to CD toxins A and B) and placebo, without MK-3415 (MA to CD toxin A) as an active comparator. Specifically, the design of this Study P002 differed from that of the earlier Study P001 in:

- Having three groups instead of four (no MK-3415, MA to CD toxin A): (1) MK-6072 (bezlotoxumab, N = 407), (2) MK-3415A (N = 397), and (3) placebo (N = 399); and
- Not having an adaptive study design, but instead subjects completing Week 12 being able to continue into the 12-month open-label safety extension phase.

III. INSPECTION OUTCOMES

	Inspected Entity	Study / Site	Outcome
1	Richard Nathan, M.D. Martha Buitrago, M.D. 2900 Cortez Falls Idaho Falls, Idaho	Site 102540 P001: 77 subjects P002: 7 subjects	March 21 – April 1, 2016 VAI*
2	Thomas Birch, M.D. 718 Teaneck Road Teaneck, New Jersey	Site 113098 P002: 62 subjects	February 29 – March 3, 2016 NAI
3	Helle Merete Staugaard, M.D. University of Copenhagen Niels Andersensvej 65 2900 Hellerup, Denmark	Site 145957 P001: 32 subjects	April 4 - 8, 2016 VAI*
4	Oliver Cornely, M.D. Innere Medizin Studienzentrum Kerpener Strasse 62 50937 Koln, Germany	Site 110101 P001: 22 subjects P002: 29 subjects	April 11 - 15, 2016 NAI*
5	Merck Research Laboratories UG2D-68, PO Box 1000 North Wales, Pennsylvania	P001 and P002	March 31 – April 12, 2016 VAI*

NAI = No Action Indicated (no significant deviations from GCP regulations)
VAI = Voluntary Action Indicated (minor deviations from GCP regulations)
OAI = Official Action Indicated (significant deviations from GCP regulations and/or data unreliable)

*Except for Site 113098 (Birch), the Establishment Inspection Report (**EIR**) has not been received from the field office. The inspection outcomes shown above are based on preliminary communications with the field investigators. At EIR receipt and review, an addendum may be forwarded to the review division if any of the inspection outcomes changes or if new significant findings are discovered; otherwise, close-out correspondence with each inspected entity (copied to review division) indicates EIR review completion with confirmation of the findings as reported in this clinical inspection summary.

The CI sites were selected for inspection based on large contribution to the overall study outcome for efficacy, and: (1) Site 145957 (Denmark) in Study P001 for most deaths, SAEs, subject discontinuations, protocol violations, and subject exclusion from the primary analysis; (2) Site 110101 (Germany) in Study P002 for most deaths (>30%); and (3) Site 113098 (United States) in Study P002 as the largest site with the second most deaths. The CI site inspections consisted of:

- General study records review: study conduct (including oversight by sponsor and institutional review board), CI financial disclosure, and drug accountability;
- Subject case records review: subject screening and eligibility, informed consent, treatment compliance, AE/safety monitoring, and data verification; and
- NDA data verification: subject randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use.

1. Richard Nathan, M.D. and **Martha Buitrago, M.D.**

Study P001, Site 102540: This CI site for Study P001 consisted of two study locations (Nathan and Buitrago). At the two locations combined: 81 subjects were screened, 77 were enrolled (randomized), and 77 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 40 subjects.

Study P002, Site 102540: This CI site for Study P002 consisted of a single study location (Nathan), where seven subjects were screened, seven were enrolled (randomized), and seven completed the study. Case records were reviewed in detail for all subjects.

No significant GCP deficiencies were observed for Study P002. A Form FDA 483 was issued to each CI for the following GCP deficiency observations limited to Study P001:

- CI Nathan: not testing the stool for CD when new diarrhea ($\geq$ 3 loose stools within 24 hours) followed the initial cure of the baseline CDI, and not reporting to the sponsor this omission of stool testing as a protocol violation (nine subjects)
- CI Buitrago: (1) not testing the diarrheal stool for CDIR, and not reporting this incomplete stool testing as a protocol violation (one subject, similarly as above for CI Nathan); and (2) placebo given to two subjects (107148 and 107400) randomized to MK-6072, and reporting this treatment error only to the sponsor and not also to the IRB.

OSI Comments (see table below):

Ten subjects with incomplete stool testing were assessed as "no CDIR," apparently based on clinical judgment unconfirmed by stool testing. They received (subjects): MK-6072 (one), MK-3415 (two), MK-3415A (three), or placebo (four).

- *The sponsor reported the omission of testing as a protocol violation in the BLA, for which subjects were to be excluded from the primary efficacy analysis using the full analysis set (**FAS**).*
- *Incomplete testing for these subjects was apparently discovered by the sponsor at post-study data audit (not reported by CI), and these subjects do not appear to have been excluded from the (supportive) per-protocol analysis for this violation.*

- *This protocol violation appears to be random (treatment groups), limited (10 of 84 subjects), and unlikely to be significant to the overall primary study outcome.*

The two subjects given the wrong study medication at the Buitrago location (placebo instead of MK-6072) were excluded from analyses.

These cited deficiencies for Study P001 are summarized in the table below: (1) affected subjects, (2) CI site locations, (3) assigned and actual treatments, (4) CDIR outcome assessment, (5) protocol violations, and (6) potential impact on data interpretability.

<table>
<tr><th>Subject</th><th>Location</th><th>Group / Treatment</th><th>CDIR</th><th>Violation</th><th>Data</th></tr>
<tr><td>107371</td><td rowspan="10">Nathan</td><td>MK-6072 / MK-6072</td><td rowspan="12">no</td><td rowspan="12">incomplete stool testing for CDI</td><td rowspan="12">assessment as no CDIR
not supported by adequate stool testing</td></tr>
<tr><td>106600
106762</td><td rowspan="2">MK-3415 / MK-3415</td></tr>
<tr><td>106462
106490
106777</td><td rowspan="3">MK-3415A / MK-3415A</td></tr>
<tr><td>106546
106651
106893</td><td rowspan="3">placebo / placebo</td></tr>
<tr><td>106705</td><td rowspan="3">Buitrago</td></tr>
<tr><td>107148</td><td rowspan="2">MK-6072 / placebo</td><td rowspan="2">wrong treatment</td><td rowspan="2">excluded (per-protocol)</td></tr>
<tr><td>107400</td><td>yes</td></tr>
</table>

Overall, study conduct at this CI site appeared acceptable, including sponsor and IRB oversight of study conduct. All audited data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the BLA.

2. Thomas Birch, M.D.

Study P002, Site 113098: 62 subjects were screened, all were enrolled (randomized), and all completed the study. Case records were reviewed in detail for 13 subjects.

No significant GCP deficiencies were observed and a Form FDA 483 was not issued. The following verbally discussed deficiency observations were considered minor, isolated, and unlikely to be significant:

- For two subjects, unbound photocopies of the diarrhea diary were used (given to the subjects for self-recording). This recordkeeping practice was considered a protocol violation (not recognized, documented, or reported).
- Two minor data discrepancies (between stool log and CRF) appeared to be isolated data transcription errors with no apparent impact on data reliability.
- Subjects 059 and 006: AE documentation lacked the subject's complaint, in addition to the diagnosis for the AE.
- Subject 045: The assigned 42 mL dose of the study medication was obtained (presumably entirely) from a single vial with (labeled) content volume of 40 mL, although two vials had been allocated to ensure the full 42 mL dose. This pharmacy practice was considered a protocol violation (not recognized, documented, or reported).

Study conduct at this CI site appeared acceptable, including sponsor and IRB oversight of study conduct. All audited data were adequately verifiable against source records and CRFs. The data from this study site appear reliable as reported in the BLA.

3. Helle Merete Staugaard, M.D.

Study P001, Site 145957: 110 subjects were screened, 32 were enrolled (randomized), and 22 completed the study. The subjects screened at this CI site had serious underlying illnesses. Despite highly selective subject screening to include the ability to complete the study, nine of the 32 enrolled subjects died of the underlying illness. Case records were reviewed for all enrolled subjects, including detailed review for nine subjects.

A Form FDA 483 was issued (b) (4)

(b) (4)

These deficiencies appear unlikely to be significant. Study conduct otherwise appeared acceptable, including sponsor and IRB oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs. The data from this study site appear reliable as reported in the BLA.

4. Oliver Cornely, M.D.

Study P001, Site 110101: 24 subjects were screened, 22 were enrolled (randomized), and 16 completed the study. The enrolled subjects had serious underlying illnesses and six did not complete the study: four died from complications of the underlying illness, one withdrew consent, and one was lost to follow up. Case records were reviewed for all enrolled subjects, including detailed review for six subjects completing study.

Study P002, Site 110101: 29 subjects were screened, all were enrolled (randomized), and 15 completed the study. The enrolled subjects had serious underlying illnesses and 14 did not complete the study: eight died from complications of the underlying illness and six withdrew consent. Case records were reviewed for all subjects, including detailed review for seven subjects completing study.

No significant GCP deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared acceptable, including sponsor and IRB oversight of study conduct. All audited data were adequately verifiable against source records and CRFs. The data from this study site appear reliable as reported in the BLA.

5. Merck Research Laboratories

This sponsor inspection consisted of: (1) general records review to evaluate compliance with GCP regulations as applicable to the sponsor, including internal data audit, database management, and systems/software validation; and (2) review of CI site training and monitoring records for Studies P001 and P002, including a detailed review for the four inspected CI sites (linked with this sponsor inspection).

A Form FDA 483 was issued (b) (4)

(b) (4)

These deficiencies appear unlikely to be significant. The sponsor's oversight of Studies P001 and P002 at the four inspected CI sites (linked with this sponsor inspection) appears to be adequately GCP-compliant.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DAIP / Division Director / Sumathi Nambiar
DAIP / Medical Team Leader / Dmitri Iarikov
DAIP / Medical Officer / Shrimant Mishra
DAIP / Regulatory Project Manager / Chris Davi

OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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

/s/

JONG HOON LEE
05/11/2016

JANICE K POHLMAN
05/12/2016

KASSA AYALEW
05/12/2016

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 2, 2016
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	BLA 761046
Product Name and Strength:	Bezlotoxumab for injection 1,000 mg/40 ml (25 mg/mL)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck & Co., Inc.
Submission Date:	November 17, 2015
OSE RCM #:	2016-21
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1. REASON FOR REVIEW

The Division of Anti –Infective Products (DAIP) requested that we review the container label, carton labeling, and Full Prescribing Information (FPI) for bezlotoxumab injection, (See Appendix G) to determine if they are acceptable from a medication error perspective.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and Full Prescribing (FPI) Information to identify deficiencies that may lead to medication errors and areas for improvement.

Our review of the container labels and carton labeling identified areas of improvement to increase clarity, prominence, and readability of important information (see Section 4.2). Our review of the prescribing information identified error-prone abbreviations, error prone trailing zeros that may pose confusion to the prescriber. We also noted that dosing instruction states (b) (4) frequency with no information on whether (b) (4) is per infection cycle or lifetime dose. We are concern since the product has a long half like ($t_{1/2}$ is about 3 weeks). We have provided a detailed summary in section 4.1 for review and consideration by DAIP.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product (See section 4.1 and section 4.2).

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ANTI- INFECTIVE PRODUCTS (DAIP)

DMEPA concludes that the prescribing information (FPI) for bezlotoxumab injection can be improved to increase clarity and prominence of important information to promote safe use of this product.

A. **General Comment**

1. Revise the "IV" abbreviations to the word "intravenous", as the abbreviation "IV" has been identified on the Institutes for Safe Medications Practices (ISMP's) list of error-prone abbreviations[1,2].

B. Prescribing Information

A. Highlights of PI under DOSAGE AND ADMINISTRATION:

1. We note that the dosing instructions state "10 mg/kg (b) (4) as an intravenous infusion over 60 minutes as a single dose." However, it does not specify if this is once a lifetime dose or once per CDI diagnosis. Since the product has a long half-life ($t_{1/2}$ is about 3 weeks), we recommend DAIP clarify the dosing frequency instruction further to promote the safe use of the product and consider revising it to read "The recommended dose of TRADEMARK is 10 mg/kg based on patient body weight administered as an intravenous infusion over 60 minutes as a one-time dose per xxxxxx" where xxxxxx is the frequency determined by DAIP for safe use of this product.

2. Revise the statement (b) (4) to read ".Dilute prior to intravenous infusion. Administer via low-protein binding 0.2 micron to 5 micron in-line or add-on filter. *See Full Prescribing Information for instructions for dilution*" for clarity and prominence of this important administration information.

B. Dosage and administration:

1. See A.1 above.

---

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Line 479. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[2] Institute for Safe Medication Practices (ISMP)'s List of Error-Prone Abbreviations, Symbols, and Dose Designations. Available from http://www.ismp.org/tools/errorproneabbreviations.pdf

4.2 RECOMMENDATIONS FOR MERCK & CO., INC.

We recommend the following be implemented prior to approval of this BLA 761046:

A. General Comment

1. Update all labels and labeling to reflect the approved proprietary name for bezlotoxumab injection and submit revised labels and labeling once the approved proprietary name has been added.

B. **Carton labeling**

1. The NDC number on the container label and carton labeling is usually the same when the quantity within the carton is equal to the quantity in the container. We note that the carton labeling has NDC 0006-3025-00 and the container label NDC 000-3025-01. Consider revising to have the same NDC number on the carton and container or provide your rationale for having different NDC numbers.

C. Container label (vial)

1. See B.1 above.
2. Relocate "RX only" statement to upper right quadrant of the principal display panel to make room for the cautionary statement "Dilute before use" on the **principle display panel** to minimize the risk of the product being administered without dilution[3].

[3] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Lines 491-492. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bezlotoxumab for injection that Merck & Co., Inc. submitted on November 17, 2015.

Table 2. Relevant Product Information for bezlotoxumab injection	
Initial Approval Date	N/A
Active Ingredient	bezlotoxumab
Indication	Indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.
Route of Administration	intravenous
Dosage Form	Solution for Injection
Strength	1,000 mg/40 mL (25 mg/mL)
Dose and Frequency	10 mg/kg based on patient body weight as an intravenous infusion over 60 minutes as a single dose.
How Supplied	1,000 mg/40 mL (25 mg/mL) solution in 50 mL vial.
Storage	Store in a refrigerator, 2°C to 8°C (36°F to 46°F). Store in original carton. Protect from light.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SEVAN H KOLEJIAN
03/02/2016

BRENDA V BORDERS-HEMPHILL
03/02/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761046

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Zinplava (bezlotoxumab) injection for intravenous infusion

Applicant: Merck Sharpe and Dohme, Inc.

Receipt Date: November 23, 2015

Goal Date: July 23, 2016

1. Regulatory History and Applicant's Main Proposals

The applicant has submitted a biologic licensing application for bezlotoxumab in the treatment of *Clostridium difficile* infection (CDI) recurrence.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *None*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *None*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *None*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *None*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *None*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *None*

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required

• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *None*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment: *None*

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment: *None*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment: *None*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *None*

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *None*

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment: *None*

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment: *None*

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment: *None*

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *None*

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment: *N/A*

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment: *N/A*

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *None*

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment: *None*

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

(insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment: *None*

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment: *None*

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *None*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment: *None*

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment: *None*

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *None*

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *None*

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: *None*

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *None*

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *None*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *None*

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment: *None*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment: *None*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment: *None*

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment: *None*

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment: *None*

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment: *None*

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *None*

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *None*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *None*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *None*

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JOSEPH C DAVI
02/02/2016