CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213138Orig1s000

OTHER REVIEW(S)

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)

Date of This Memorandum:	January 9, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213138 and NDA 201699/S-012
Product Name and Strength:	Dificid (fidaxomicin) for Oral Suspension, 40 mg/mL
Applicant/Sponsor Name:	Cubist Pharmaceuticals, LLC (Cubist)
OSE RCM #:	2019-1561-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 8, 2020 for Dificid. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Dificid (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

In our previous Label and Labeling Review Memo we recommended that Cubist revise the National Drug Code (NDC) on their container label, as well as the pouch and carton labeling, using different NDC package code numbers (last digit(s) of the NDC). Additionally, we recommended to the Division that references to "(b) (4)" as the diluent for reconstitution be revised to read, "Purified Water."[a]

On December 19, 2019, our labeling recommendation, regarding the NDC package codes, was communicated to Cubist.[b]

[a] Myers D. Label and Labeling Review Memo for Dificid (NDA 213138 and NDA 201699/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 26. RCM No.: 2019-1561-1.
[b] Park, K. FDA Communication: sNDA 201699/S-012 & NDA 213138 (Dificid) - DMEPA Information Request re: Carton/Container Labeling (Response requested by 1/8/2020). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2019 DEC 19. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80531ccc

On December 28, 2019, Cubist requested our rationale for having the same NDC on all levels packaging. On December 30, 2019, DMEPA provided clarification, after consulting with the Electronic Drug Registration and Listing team, that we find Cubist's proposal to use different package codes acceptable.[c]

On January 8, 2020, Cubist submitted revised versions of the carton, bottle, and pouch labels which included changing from '(b) (4)' to 'purified water' to align with the changes requested in the prescribing information. Additionally, Cubist notes that after requesting clarification from DMEPA on December 28, 2019, the NDC on each level of packaging remains unchanged.[d]

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[c] Park, K. FDA Communication: sNDA 201699/S-012 & NDA 213138 (Dificid) - DMEPA Information Request re: Carton/Container Labeling (Response requested by 1/8/2020). Silver Spring (MD): FDA, CDER, OND, DAI (US); 2019 DEC 30. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80533f6b

[d] Cover Letter (NDA 201,699:/Supplement 012 DIFICID® (fidaxomicin) tablets Amendment to Pending Supplement: Proposed Revised Labeling Waiver of the one-half page Highlights Requirement. Lucerne (Switzerland): Cubist Pharmaceuticals LLC; 2020 JAN 08. Available from: \\cdsesub1\evsprod\nda201699\0182\m1\us\cover-letter.pdf

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OTTO L TOWNSEND
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Clinical Inspection Summary

Date	1/7/2020
From	Karen Bleich, MD, Acting Team Leader Phillip Kronstein, MD, Acting Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kristine Park, PhD, RAC, Regulatory Project Manager Rama Kapoor, MD, Clinical Reviewer Edward Weinstein, MD, PhD, Clinical Team Leader Division of Anti-Infective Products
NDA/BLA #	NDA 201699/S012
Applicant	Cubist Pharmaceuticals LLC/ Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Drug	Fidaxomicin (DIFICID)
NME (Yes/No)	No
Review Classification	Priority
Proposed Indication(s)	Treatment of Clostridium difficile-associated diarrhea in patients aged ≥6 months of age
Consultation Request Date	8/27/2019
Summary Goal Date	12/31/2019
Action Goal Date	1/24/2020
PDUFA Date	1/24/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study 2819-CL-0202 was submitted to the Agency in support of Supplement 12 for NDA 201699 to expand the indication for Dificid to include treatment of *Clostridioides difficile*-associated diarrhea (CDAD) in patients aged ≥6 months of age. Two clinical sites from the study were selected for audit: Dr. Krisztina Kalocsai (Site 36006) and Dr. Josh Wolf (Site 10022). The sites selected were among the highest enrollers of study subjects, and thus contributed significantly to the overall efficacy determination.

On-site inspections demonstrated no significant findings at either of the audited sites related to data integrity or human subject protection. There was no evidence of underreporting of adverse events. Based on the inspections, Study 2819-CL-0202 appears to have been conducted adequately, and the data generated by the inspected clinical sites appear acceptable in support of the proposed indication.

II. BACKGROUND

Cubist Pharmaceuticals LLC/ Merck Sharp & Dohme Corp. seeks approval to market Dificid for the treatment of *Clostridioides difficile*-associated diarrhea (CDAD) in children aged ≥6 months of age. Dicifid has bactericidal activity against *C. difficile* and was approved by the FDA in May 2011 for the treatment of CDAD in adults.

The clinical data to support the additional use of Dificid in children aged ≥6 months of age includes the Phase 3 Study 2819-CL-0202, a prospective, multi-center, randomized trial to evaluate the safety and effectiveness of Dificid compared to vancomycin for the treatment of CDAD in children ≥6 months of age.

The study is summarized below:

Study 2819-CL-0202 ("The SUNSHINE Study")

Title of Study: "A Phase 3, multicenter, investigator-blind, randomized, parallel group study to investigate the safety and efficacy of fidaxomicin oral suspension or tablets taken q12h, and Vancomycin oral liquid or capsules taken q6h, for 10 days in pediatric subjects with *Clostridium difficile*-associated diarrhea."
Number of subjects (FAS, SAF): 142
Number of sites: 74 sites in 11 countries (U.S., Poland, France, Germany, Romania, Hungary, Spain, Italy, Belgium, Canada, and Slovakia)
Study Period: January 9th, 2015 – March 7th, 2018
Main criteria for inclusion: Children ≥6 months of age to <18 years of age diagnosed with CDAD according to local diagnostic criteria
Treatment administration: Subjects randomized 2:1 to Arm 1 or Arm 2
Arm 1: Dificid oral suspension 32 mg/kg/d, divided in 2 doses/d, for 10 days; or Dificid 200 mg tables, 2 times daily for 10 days
Arm 2: Vancomycin oral liquid 40 mg/kg/d, divided in 4 doses/d, for 10 days; or vancomycin 125 mg capsules 4 times daily for 10 days
Primary Objective:
To investigate the clinical response of Dificid granules for oral suspension or tablets and vancomycin oral liquid or capsules of pediatric subjects ≥6 months of age with CDAD.
Primary Efficacy Endpoint:
Confirmed clinical response (CCR) based on the assessment by the investigator (at EOT +2 days TC/visit)

III. RESULTS (by site):

1. Krisztina Kalocsai, Budapest, Hungary (Site 36006)
The inspection of Dr. Kalocsai's site was conducted from 12/2/2019 – 12/5/2019. At the time of the inspection, the study was completed. The site screened 14 subjects and enrolled 14 subjects.

The inspection included a review of documents related to the site's Ethics Committee approval and correspondences, informed consent, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all 14 enrolled subjects was performed, including consent, adverse events, and primary endpoint data. The data listings submitted in the NDA were verified by comparison with the source data at the site. The primary endpoint data was verified and there was no evidence of under-reporting of AEs or protocol violations.

The following concomitant medication information was present in the source data and absent in the NDA submission:

- Subject (b) (6) Lioton (topical, for shoulder pain)
- Subject Vigantol *(Vitamin D)*
- Subject Magnesium citrate
- Subject Mycostatin 2 x 200mg IV, Dicynone 3 x 1 amp, Aminoven 10% 250 mL IV, Dipeptiven 40 mL IV

Reviewer's Note*: The medications listed above are from the hospital notes available at the study site. The ORA field inspector did not have access to additional information regarding dosing and indications.*

No significant deficiencies were identified at the site. Other than the concomitant medications listed above for 4 subjects at the site, there were no significant inconsistencies between source records and submitted NDA data. No FDA Form 483 was issued at the end of the inspection.

Reviewer's Note*: An amendment to this inspection summary will be issued if the EIR for Dr. Krisztina Kalocsai, expected to become available in a few weeks, contains considerable differences from the preliminary report.*

2. Josh Wolf, Memphis, Tennessee (Site 10022)

The inspection of Dr. Wolf's site was conducted from 11/19/2019 – 11/21/2019. At the time of the inspection, the study was completed. The site screened 29 subjects and enrolled 28 subjects. 26 subjects completed the study; one subject withdrew, and another subject died.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, site monitoring, investigational product accountability, and financial disclosures. Significant financial disclosures at the site are consistent with documentation submitted in the NDA submission (Section 1.3.4 Financial Certification and Disclosure). The inspection also included a review of electronic records and electronic signatures.

A comprehensive review of the source document records regarding consent, adverse events,

and primary endpoint data was performed for all 28 enrolled subjects. Source records of fourteen of the subjects were additionally reviewed for eligibility criteria, protocol conduct, and concomitant medications. The data listings submitted in the NDA were verified by comparison with the source data at the site. The primary endpoint data was verified, and there was no evidence of under-reporting of AEs or protocol violations.

No significant deficiencies were identified at the site and no significant inconsistencies between source records and submitted NDA data were identified. No FDA Form 483 was issued at the end of the inspection.

{See appended electronic signature page}

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

CONCURRENCE: {See appended electronic signature page}

Phillip Kronstein, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.
Review Division /Division Director/Sumathi Nambiar
Review Division /Medical Team Leader/Edward Weinstein
Review Division /Project Manager/Kristine Park
Review Division/MO/Rama Kapoor
OSI/Office Director/David Burrows
OSI/DCCE/ Division Director/Ni Aye Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Acting Branch Chief/Phillip Kronstein
OSI/DCCE/Team Leader/Karen Bleich
OSI/DCCE/GCP Reviewer/Karen Bleich
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters

APPEARS THIS WAY ON ORIGINAL

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/s/

KAREN B BLEICH
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Note that this document corrects an error in the previous Clinical Inspection Summary dated 12/23/2019. The indication is for patients greater than or equal to 6 months of age, not as previously stated 6 years of age.

PHILLIP D KRONSTEIN
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Clinical Inspection Summary

Date	12/21/2019
From	Karen Bleich, MD, Acting Team Leader Kassa Ayalew, MD, MPH, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kristine Park, PhD, RAC, Regulatory Project Manager Rama Kapoor, MD, Clinical Reviewer Edward Weinstein, MD, PhD, Clinical Team Leader Division of Anti-Infective Products
NDA/BLA #	NDA 201699/S012
Applicant	Cubist Pharmaceuticals LLC/ Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Drug	Fidaxomicin (DIFICID)
NME (Yes/No)	No
Review Classification	Priority
Proposed Indication(s)	Treatment of Clostridium difficile-associated diarrhea in patients aged ≥6
Consultation Request Date	8/27/2019
Summary Goal Date	12/31/2019
Action Goal Date	1/24/2020
PDUFA Date	1/24/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study 2819-CL-0202 was submitted to the Agency in support of Supplement 12 for NDA 201699 to expand the indication for Dificid to include treatment of Clostridium difficile-associated diarrhea (CDAD) in patients aged ≥6 years of age. Two clinical sites from the study were selected for audit: Dr. Krisztina Kalocsai (Site 36006) and Dr. Josh Wolf (Site 10022). The sites selected were among the highest enrollers of study subjects, and thus contributed significantly to the overall efficacy determination.

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

CONCURRENCE: {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:

Central Doc. Rm.
Review Division /Division Director/Sumathi Nambiar
Review Division /Medical Team Leader/Edward Weinstein
Review Division /Project Manager/Kristine Park
Review Division/MO/Rama Kapoor
OSI/Office Director/David Burrows
OSI/DCCE/ Division Director/Ni Aye Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Karen Bleich
OSI/DCCE/GCP Reviewer/Karen Bleich
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters

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/s/

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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:	December 4, 2019
To:	Kristine Park, PhD, RAC Regulatory Health Project Manager **Division of Anti-Infectives (DAI)**
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:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	David Foss, Pharm. D., MPH, BCPS, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route, Application Type/Number and Supplement Number:	DIFICID (fidaxomicin) for oral suspension, NDA 213138 DIFICID (fidaxomicin) tablets, for oral use, NDA 201699 S-012
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On July 24, 2019 Merck Sharp & Dohme Corp. submitted for the Agency's review an original New Drug Application (NDA) 213138 for DIFICID (fidaxomicin) for oral suspension. This NDA submission provides Chemistry and Manufacturing Controls (CMC) documentation to support the approval of DIFICID oral suspension for use in pediatric patients.

On October 31, 2019 the Applicant submitted an Amendment to Pending Supplement: Proposed Revised Labeling to NDA 201699 for DIFICID (fidaxomicin) tablets, for oral use. The purpose of this submission is to fulfill a Post-Marketing Requirement (PMR) issued in the approval letter for DIFICID (fidaxomicin) tablets, for oral use under the Pediatric Research Equity Act (PREA).

DIFICID (fidaxomicin) tablets, for oral use was approved on May 27, 2011 and is a macrolide antibacterial drug indicated in adults (≥18 years of age) for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use will share a combined label.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on October 23, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use PPI received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on November 27, 2019.
- Draft DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use PPI received on July 31, 2019, revised by the Review Division throughout the review cycle, and received OPDP on November 27, 2019.
- Draft DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use Prescribing Information (PI) received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on November 27, 2019.
- Draft DIFICID (fidaxomicin) for oral suspension and DIFICID (fidaxomicin) tablets, for oral use Prescribing Information (PI) received on July 31, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on November 27, 2019.

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.

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.

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

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

Memorandum

Date: December 3, 2019

To: Rama Kapoor, M.D.
Division of Anti-Infective Products (DAIP)

Kristine Park, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for DIFICID® (fidaxomicin) tablets, for oral use and DIFICID® (fidaxomicin) for oral suspension

NDA: 201699/Supplement 012 & NDA 213138

In response to DAIP's consult request dated October 23, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for Dificid. This supplement (S012) adds a pediatric indication for Clostridium difficile-associated diarrhea (CDAD) in patients aged ≥ 6-months and older.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on November 27, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on November 27, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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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)

Date of This Memorandum:	November 26, 2019
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 213138 and NDA 201699/S-012
Product Name and Strength:	Dificid (fidaxomicin) for Oral Suspension, 40 mg/mL
Applicant/Sponsor Name:	Cubist Pharmaceuticals, LLC (Cubist) (an indirectly wholly-owned subsidiary of Merck Sharp & Dohme Corp, and a subsidiary of Merck & Co., Inc. (Merck))
OSE RCM #:	2019-1561-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 22, 2019 for Dificid. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Dificid (Appendix A) to determine 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.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. As currently presented, the revised National Drug Code (NDC) on the container label, as well as the pouch and carton labeling include different NDC package code numbers and are not aligned with the proposed prescribing information. In addition, we note references to "(b) (4)" in the labeling as the diluent to be used for reconstitution of Dificid granules. Per discussion with the Office of Pharmaceutical Quality (OPQ), "(b) (4)

[a] Myers D. Label and Labeling Review for Dificid (NDA 213138 and NDA 201699/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-1561.

(b) (4) purified water would be appropriate for reconstitution of Dificid granules.

3 RECOMMENDATIONS FOR THE DIVISION

The proposed labeling lists "(b) (4)" as the diluent to be used for reconstitution of Dificid granules. If OPQ concurs, please include the recommendation below with the other recommendation we have for Cubist.

> The proposed container label, as well as the pouch and carton labeling include the statement, "Each mL contains 40 mg fidaxomicin after reconstitution with 130 mL (b) (4)." However, (b) (4) is not required to reconstitute Dificid granules and (b) (4) may not be readily available in retail pharmacies. Please revise the statement to read, "Each mL contains 40 mg fidaxomicin after reconstitution with 130 mL Purified Water."

In addition, if OPQ concurs, we recommend references to (b) (4) be revised in the Prescribing Information to read, "Purified Water".

4 RECOMMENDATIONS FOR CUBIST PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of the original NDA and the Supplemental NDA:

> Your revised National Drug Code (NDC) on the container label, as well as the pouch and carton labeling include different NDC package code numbers (last digit(s) of the NDC) (i.e., -1 for the container label, -2 for the carton labeling, and -3 for the pouch). One carton, containing one unit, should have the same NDC numbers (last digit(s) of the NDC). Therefore, to align with your proposed prescribing information (PI), as well as the container label, update the NDC for the pouch and carton labeling to be 52015-7002-1

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

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OTTO L TOWNSEND on behalf of DEBORAH E MYERS
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11/26/2019 03:47:01 PM

LABEL AN 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:	November 15, 2015
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 213138 and NDA 201699/S-012
Product Name and Strength:	Dificid (fidaxomicin) for Oral Suspension, 40 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Cubist Pharmaceuticals, LLC (Cubist) (an indirectly wholly-owned subsidiary of Merck Sharp & Dohme Corp, and a subsidiary of Merck & Co., Inc. (Merck))
FDA Received Date:	July 24, 2019, August 22, 2019, October 31, 2019, and November 12, 2019
OSE RCM #:	2019-1561
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Dificid (fidaxomicin) for Oral Suspension, the Division of Anti-Infective Products (DAIP) requested that we review the proposed Dificid prescribing information (PI), patient package insert (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 213138 is a 505(b)(1) application submitted on July 24, 2019. NDA 213138 was submitted in conjunction with and cross-referenced to the efficacy supplement (sNDA) submitted under NDA 201699 (Dificid tablets) to support the Dificid pediatric indication for *Clostridium difficile*-associated diarrhea (CDAD) in patients 6 months of age and older. This sNDA is being submitted to fulfill a Post-Marketing Requirement (PMR) 1757-002 that was issued in the approval letter for Dificid (NDA 201699) on May 27, 2011, under the Pediatric Research Equity Act (PREA).

Included in the July 24, 2019, Submission Cover Letter for NDA 213138 is a statement that "all labeling components for Dificid for Oral Suspension may be located in the efficacy supplement under NDA 201699."

Subsequently, on August 22, 2019 and October 31, 2019, Amendments to Pending Supplement: Proposed Revised Labeling were submitted to NDA 201699/S-012.

Subsequently, on November 12, 2019, an Amendment to Pending Supplement: Proposed Revised Labeling was submitted to NDA 201699/S-012, which is cross-referenced with the Quality Information Amendment – Response to Agency Questions[a] submitted under NDA 213138.

3 MATERIALS 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	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A

[a] Quality Information Amendment – Response to Agency Questions for Dificid (NDA 213138). Lucerne (Switzerland): Cubist Pharmaceuticals, LLC; 2019 NOV 12. Available from: \\cdsesub1\evsprod\nda213138\0008\m1\us\cmc\quality-information-amendment-12nov2019.pdf.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	F

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

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), patient package insert (PPI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information – *Dosage Forms and Strengths*			
1.	As currently presented, the strength for the oral suspension is stated as "200 mg/5 mL when reconstituted"; however, does not include the "40 mg/mL" strength statement that is included in Section 3 of the PI, *Dosage Forms and Strengths*, Table 1, included in Section 2,	Inconsistent product strength statements could lead to confusion as well as wrong strength medication errors.	Product strength statements should include consistent units of measure across all elements of the labeling (e.g., container, carton, and prescribing information).[b] To decrease the potential for wrong strength/dose medication errors and to align with the strength statement (i.e., 40 mg/mL) on the proposed container and carton labeling,

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf (lines 380 - 381).

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Dosage and Administration, as well as the proposed container and carton labeling.		we recommend the consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI. For example, change the current statement, "For oral suspension: 200 mg/5 mL when reconstituted." to instead "For oral suspension: 40 mg/mL (200 mg/5 mL) when reconstituted."
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented, no information is provided regarding use of the "for oral suspension" dosage form for adult patients who are unable to swallow tablets or administration via feeding (i.e., nasogastric, gastrostomy, etc.) tubes.	As the "for oral suspension" dosage form may be used for adult patients who are unable to swallow tablets or administered via feeding tubes, appropriate dosage and administration instructions should be provided.	We defer to the Dificid team to determine if the "for oral suspension" dosage form is an appropriate dosage form for adult patients who are unable to swallow tablets and/or to be administered via feeding tubes, and thus to be included in the prescribing information (PI), as well as implementation of any appropriate corresponding updates in the PI.
2.	As currently presented, under Section 2.1, (b) (4) , the strength of tablets is included (i.e., 200 mg); however, the strength for the oral suspension is not included.	Inconsistent product strength statements could lead to confusion as well as wrong strength medication errors.	To provide consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI, we recommend incorporating "40 mg/mL when reconstituted." For example, "Dificid is available for oral administration as 200 mg tablets and as granules for oral suspension (40 mg/mL (200

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			mg/5 mL) when reconstituted)."
3.	As currently presented, under Section 2.4, subsection "Administration" the third statement is "Remove cap, then administer orally with or without food using an oral dosing (b) (4) ."	Yin et al., found that use of oral syringes was associated with less dosing errors than oral dosing cups.[c]	Change the terminology "oral dosing (b) (4) " in Section 2.4, to instead "oral dosing syringe." For example, "Remove cap, then administer orally with or without food using an oral dosing syringe."
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the strength statement is "each 5 mL…contains 200 mg of fidaxomicin (40 mg of fidaxomicin per mL)."	Inconsistent product strength statements could lead to confusion as well as wrong strength medication errors.	To decrease the potential for wrong strength/dose medication errors and to align with the proposed container label and carton labeling, we recommend the consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI. For example, in Section 3, we recommend switching the current order to instead, "each mL …contains 40 mg of fidaxomicin (200 mg of fidaxomicin per 5 mL)."
Full Prescribing Information – Section 16.1 *How Supplied*			

[c] Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. Pediatrics. 2016; 138(4): e20160357.

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the concentration of fidaxomicin is stated as "200 mg per 5 mL (40 mg/mL) in the reconstituted oral suspension."	Inconsistent product strength statements could lead to confusion as well as wrong strength medication errors.	To decrease the potential for wrong strength/dose medication errors and to align with the proposed container label and carton labeling, we recommend the consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI. For example, we recommend switching the current order to instead, "The concentration of fidaxomicin is 40 mg per mL (200 mg/5 mL) in the reconstituted oral suspension."
3.	As currently presented, under the subsection "Granules for oral suspension" no information is included to reinforce that any remaining unused portion should be discarded after 12 days.	The remaining suspension could be "saved" for future use resulting in use of deteriorated drug product medication errors.	Following the current statement "After reconstitution, the total oral suspension volume is 136 mL." add the statement "Discard unused suspension after 12 days." For example, "After reconstitution, the total oral suspension volume is 136 mL. Discard unused suspension after 12 days. The concentration of fidaxomicin is 200 mg per 5 mL (40 mg/mL) in the reconstituted oral suspension."
Full Prescribing Information – Section 17 *Patient Counseling Information*			
1.	As currently presented, no statement is present	Yin et al., found that use of oral syringes was associated	Add a subsection "Oral Suspension" that includes the

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	to instruct patients, or their caregivers, to use an oral dosing syringe to measure the appropriate dose.	with less dosing errors than oral dosing cups.[d]	following statements: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients or caregivers that oral dosing syringes may be obtained from their pharmacy."
2.	Section 2.4, subsection "Administration" includes the instruction "Remove the bottle from the refrigerator 15 minutes prior to each administration." As currently presented, Section 17, *Patient Counseling Information*, lacks this helpful information.	Omission of information necessary for patients to use the drug safely and effectively may result in medication errors.	Under the new subsection, "Oral Suspension", consider including the instruction "Remove the bottle from the refrigerator 15 minutes prior to each administration."
Patient Package Insert (PPI)			
1.	As currently presented, the term "child" is used throughout the "How do I take Dificid?" subsection of the PPI.	This "for oral suspension" dosage form may be used for adult patients who are unable to swallow tablets or who would have it administered via feeding tubes.	If it is determined that the "for oral suspension" dosage form is an appropriate dosage form for adult patients, then the "How do I take Dificid" subsection will need to be revised to reflect administration in both pediatric and adult patients.
Container Label and Carton Labeling			

[d] Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. Pediatrics. 2016; 138(4): e20160357.

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the statement "For pediatric use." appears on the container label, as well as the pouch and carton labeling.	This "for oral suspension" dosage form may be used for adult patients who are unable to swallow tablets or administered via feeding tubes.	If it is determined that the "for oral suspension" dosage form is an appropriate dosage form for adult patients, then to align with changes made to the "Dosage and Administration" section of the PI, we will need to be update and/or remove the statement "For pediatric use." from the container label, as well as the pouch and carton labeling.
3.	As currently presented, "…after reconstitution with 130 mL (b) (4) ." appears on container label, as well as the pouch and carton labeling. Additionally, Section 2.4 of the PI includes for preparation, "Measure 130 mL of (b) (4) …"	The labeling submitted on November 12, 2019, changed the term "water" to "(b) (4)" throughout the labeling. As (b) (4) is not routinely stocked and used in retail pharmacies, and instead purified (i.e. distilled) water is normally used by pharmacists for the reconstitution of liquid oral dosage forms.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine if the use of water is appropriate for reconstitution and if so to provide the recommendation to change the term "(b) (4) " to "water" in Section 2.4 of the PI, as well as the container label and carton labeling.
4.	As currently presented, the statement "Store in the original bottle." appears on the container label and the statements "Store in the original package." and "Do not open pouch until time of use." appear on the pouch and carton labeling.	Improper product storage could lead to deteriorated drug medication errors.	We defer to OPQ to determine if the inclusion of the statement "Store in the original bottle." is appropriate for inclusion on the container label and if the statements "Store in the original package." and "Do not open pouch until time of use." are appropriate for inclusion on the pouch and carton labeling.

Table 3. Identified Issues and Recommendations for Cubist Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXXX-X).		Your proposed prescribing information (PI) includes the NDC as 52015-7002-1. If the NDC of 52015-7002-1 is correct, add this NDC to the container label, as well as the pouch and carton labeling and submit for our review.
Container Label			
1.	As currently presented, the statement "(b) (4) appears on the container label, as well as the pouch and carton labeling.	Once the product is reconstituted by a pharmacist, the unused contents must be discarded after 12 days. If the user misses this discard information, it could result in the administration of deteriorated product or wrong duration medication errors.	To increase the prominence of the discard information, we recommend rephrasing and moving the statement "(b) (4) to the principal display panel (PDP) following the current statement "MUST BE RECONSTITUTED BY A PHARMACIST BEFORE DISPENSING." on the PDP. Additionally, we recommend including a space for healthcare providers to add the date that the product should be discarded. In addition, we recommend changing the color of the font, surrounding this information with a box, and/or highlighting the information to draw attention to this important information (see example below):

Table 3. Identified Issues and Recommendations for Cubist Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"MUST BE RECONSTITUTED BY A PHARMACIST BEFORE DISPENSING." Discard unused portion after ____/____/____.
Carton Labeling			
1.	As currently presented, the intended location of the machine-readable, 2D data matrix barcode product identifier, on the smallest saleable unit (usually the carton), is not included on the carton labeling.	The drug package label must include the product identifier information (i.e., the NDC, serial number, lot number, and expiration date) in both the human-readable form and machine-readable, 2D data matrix barcode format.	We recommend you include the intended location of the machine-readable, 2D data matrix barcode product identifier, near the human-readable portion of the product identifier information (i.e., NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]). See draft guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf (Lines 255 - 283).

5 CONCLUSION

Our evaluation of the proposed Dificid prescribing information (PI), patient package insert (PPI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Cubist Pharmaceuticals, LLC so that recommendations are implemented prior to approval of the original NDA and the Supplemental NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Dificid that Cubist Pharmaceuticals, LLC, submitted on November 12, 2019.

Table 4. Relevant Product Information for Dificid (NDAs 213138 and 201699)		
Product Name	Dificid (NDA 213138)	Dificid (NDA 201699)
Initial Approval Date	Not Applicable	May 27, 2011
Active Ingredient	fidaxomicin	
Indication	for the treatment of (b) (4) in adults and pediatric patients aged 6 months and older.	
Route of Administration	oral	
Dosage Form	Granules, for Oral Suspension	tablets
Strength	40 mg/ mL (200 mg/5 mL) when reconstituted	200 mg
Dose and Frequency	Dificid is administered orally with or without food.	
	The recommended doses for pediatric patients based on weight are shown in the Table below. Dificid oral suspension should be administered orally twice daily for 10 days. Recommended Dosage of DIFICID Oral Suspension in Pediatric Patients, Based on Weight Body Weight / Dose / Volume of 40 mg/mL Suspension to be Administered Orally 4 kg to less than 7 kg / 80 mg twice daily / 2 mL twice daily 7 kg to less than 9 kg / 120 mg twice daily / 3 mL twice daily 9 kg to less than 12.5 kg / 160 mg twice daily / 4 mL twice daily 12.5 kg and above / 200 mg twice daily / 5 mL twice daily	<u>Adults</u>: The recommended dose for adults is one 200 mg tablet orally twice daily for 10 days. <u>Pediatrics (6 months to less than 18 years of age)</u>: The recommended dose for pediatric patients weighing at least 12.5 kg and able to swallow tablets is one 200 mg tablet orally twice daily for 10 days. If unable to swallow tablets, pediatric patients may be dosed with Dificid oral suspension as recommended in the table to the left.
How Supplied	A 150 mL amber glass bottles of 9.53 g of granules that contain 5.45 g of fidaxomicin (NDC 52015-7002(b) (4)). Each glass bottle has a child-resistant cap and is sealed in a laminated aluminum foil	Bottles of 20 tablets (NDC 52015-080-01).

	pouch. After reconstitution, the total oral suspension volume is 136 mL. The concentration of fidaxomicin is 200 mg per 5 mL (40 mg/mL) in the reconstituted oral suspension.	
Storage	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). Store in the original package. Do not open pouch until time of use. Once reconstituted, store DIFICID oral suspension refrigerated at 2°C-8°C (36°F-46°F) for up to 12 days. Store capped in the original bottle.	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). See USP controlled room temperature. Store in the original bottle.
Container Closure	150 mL Amber Glass Bottle, with 28 mm, white child resistant cap with (b) (4) liner, and enclosed in a laminated aluminum foil pouch.	White, high density polyethylene (HDPE) bottles with (b) (4) caps and desiccants.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 7, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, "Dificid" and "fidaxomicin." Our search identified 5 previous reviews[e,f,g,h,i], and we confirmed that our previous recommendations were implemented.

[e] Crandall, A. Proprietary Name Review for Dificid (IND 064435). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 MAY 06. RCM No.: 2008-1616.

[f] Holmes, L. Proprietary Name Review for Dificid (NDA 201699). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAR 08. RCM No.: 2010-2648.

[g] Holmes, L. Label and Labeling Review for Dificid (NDA 201699). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAR 10. RCM No.: 2010-2650.

[h] Winiarski, A. 915 Review for Dificid (NDA 201699). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 APR 18. RCM No.: 2011-2290.

[i] Shah, M. Labeling and Labeling Comprehension Study Results Review for Dificid (NDA 201699/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 01. RCM No.: 2018-2721.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Dificid labels and labeling submitted by Cubist Pharmaceuticals, LLC.

- Container label received on November 12, 2019 (submitted under NDA 201699/S-012)
- Carton labeling received on November 12, 2019(submitted under NDA 201699/S-012)
- Patient Package Insert (PPI) received on August 22, 2019 (submitted under NDA 201699/S-012)
    - Annotated PPI available at: \\cdsesub1\evsprod\nda201699\0122\m1\us\02-wrm-usppi-mk5119-mf-pediatric-os.doc
    - Proposed PPI available at: \\cdsesub1\evsprod\nda201699\0122\m1\us\02-crt-usppi-mk5119-mf-pediatric-os.doc
- Prescribing Information (PI) Revised Labeling received on November 12, 2019 (submitted to NDA 201699/S-012)
    - Annotated PI available at: \\cdsesub1\evsprod\nda201699\0162\m1\us\04-wrm-uspi-mk5119-mf-pediatric-os.doc
    - Proposed (Draft) PI available at: \\cdsesub1\evsprod\nda201699\0162\m1\us\04-crt-uspi-mk5119-mf-pediatric-os.doc

F.2 Label and Labeling Images

Container label (not to scale)

[j] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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