

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

201699Orig1s000

Trade Name: Dificid Tablet, 200 mg

Generic Name: fidaxomicin

Sponsor: Optimer Pharmaceuticals, Inc.

Approval Date: May 27, 2011

Indications: Treatment of *Clostridium difficile*-associated diarrhea in adults (≥ 18 years of age)

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APPROVAL LETTER



NDA 201699

NDA APPROVAL

Optimer Pharmaceuticals, Inc.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your New Drug Application (NDA) dated November 29, 2010, received November 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dificid (fidaxomicin) Tablet, 200 mg.

We acknowledge receipt of your amendments dated December 1, 14, and 23, 2010, and January 7, 18, and 28, February 11, April 1, 6, and 15, and May 4, 23, and 26, 2011.

This new drug application provides for the use of Dificid (fidaxomicin) Tablet for the treatment of *Clostridium difficile*-associated diarrhea in adults (≥ 18 years of age).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on May 23, 2011, as soon as they are available, but no

more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 201699.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 to less than 6 months because necessary studies are impossible or highly impractical since the disease does not occur in this population. We are deferring submission of your pediatric studies for ages 6 months to less than 18 years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below:

1757-001: Conduct a prospective clinical trial of 10 days of Difucid (fidaxomicin) in at least 32 pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea to evaluate the safety and pharmacokinetics (including serum and fecal concentrations) of Difucid (fidaxomicin).

Final Protocol Submission:	10/2011
Trial Completion:	1/2013
Final Report Submission:	4/2013

1757-002: Conduct a prospective, randomized clinical trial to demonstrate safety and effectiveness of Dificid (fidaxomicin) compared to vancomycin in pediatric patients (6 months to less than 18 years of age) with *C. difficile*-associated diarrhea.

Final Protocol Submission:	7/2013
Trial Completion:	1/2017
Final Report Submission:	7/2017

Submit the protocols to your IND 64,435 with a cross-reference letter to this NDA. Submit all final reports as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of development of bacterial resistance.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1757-003: Conduct a prospective study over a five-year period after introduction of Dificid (fidaxomicin) to the market to determine if decreased susceptibility to Dificid (fidaxomicin) is occurring in *C. difficile*. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on May 23, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	9/2011
Interim Report Submission:	2/2012
	12/2013
	12/2014
	12/2015
Study Completion:	10/2016
Final Report Submission:	3/2017

Submit the protocol to your IND 64,435 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1757-004: Conduct a prospective, randomized, comparative trial to demonstrate the efficacy of Dificid (fidaxomicin) in the treatment of patients with multiple recurrences of *C. difficile*-associated diarrhea.

The timetable you submitted on May 26, 2011, states that you will conduct this clinical trial according to the following schedule:

Final protocol submission: 1/2012
Trial completion: 11/2015
Final Report Submission: 6/2016

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

1757-005: Submit a chemistry and manufacturing controls supplement to include a test for the (b) (4) in the drug substance specification.

The timetable you submitted on May 23, 2011, states that you will conduct this study according to the following schedule:

Supplement Submission: 11/2011

Submit clinical protocols to your IND 64,435 for this product. Submit chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21

CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Fariba Izadi, Pharm.D, Regulatory Project Manager, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Carton and Container Labeling
Package Insert

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

/s/

EDWARD M COX
05/27/2011