CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward M. Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	201-699
Applicant Name	Optimer Pharmaceuticals, Inc.
Date of Submission	November 30, 2010
PDUFA Goal Date	May 30, 2011
Proprietary Name / **Established (USAN) Name**	Dificid fidaxomicin
Dosage Forms / Strength	tablet / 200 mg
Proposed Indication(s)	for treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adults (≥18 years of age)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Dmitri Iarikov
Statistical Review	Rima Izem, Scott Komo
Pharmacology Toxicology Review	Wendy Schmidt, Amy Nostrand, Abby Jacobs
CMC Review/OBP Review	Balajee Shanmuggan, Rapi Madurawe, Elizabeth Chikhale, Patrick Marroum, Terrence Ocheltree
Microbiology Review	Fred Marsik
Clinical Pharmacology Review	Aryun Kim, Kim Bergman
DDMAC	Christine Corser, Sheila Ryan
DSI	Kassa Ayalew, Lauren Iacono-Conners
CDTL Review	John Alexander
OSE/DMEPA	Loretta Holmes, Irene Chan, Carol Holquist
Deputy Division Director Review	Katherine Laessig

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Background

NDA 201-699 evaluates fidaxomicin for the treatment of *Clostridium difficile* associated diarrhea (CDAD). Fidaxomicin when taken orally remains predominantly in the gastrointestinal tract. It acts by inhibiting RNA synthesis by bacterial RNA polymerase. Vancomycin is the only antibacterial drug that is FDA approved for the treatment of CDAD.

The review team has reviewed the issues in detail for NDA 201-699 in their respective disciplines with regards to the safety and efficacy of fidaxomicin for the treatment of CDAD.

For a detailed discussion of NDA 201-699, the reader is referred to the individual discipline specific reviews. In addition Dr. Alexander's Cross-Discipline Team Leader Review and Dr. Laessig's Deputy Division Director's Review summarize key issues in the NDA submission. I concur with the recommendations of the review team that the information on safety, efficacy, and product quality for fidaxomicin support approval. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls

The chemistry manufacturing and controls are summarized in Dr. Shanmugam's Chemistry review which recommends approval from the standpoint of CMC for fidaxomicin 200 mg tablets. The ONDQA Biopharmaceutics team has reviewed the dissolution specification and arrived at an agreed upon dissolution specification. The stability data supports 24-month expiry dating at 20°C-25°C, excursions permitted a to 15°C-30°C. The Office of Compliance has an overall Acceptable recommendation for the manufacturing facilities. The approval includes a postmarketing commitment to include a test for the (b) (4) of fidaxomicin in the drug substance specification.

Pharmacology Toxicology

The recommendation from Dr. Schmidt with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. The low systemic bioavailability and low solubility of fidaxomicin and the toxicilogic effects of solubilizing agents presented challenges in the performance of toxicology studies. A mass balance study with radioactive fidaxomicin in dogs found that >85% of the dose was found in the feces. The initial attempt to perform a 3-month toxicology study in dogs using a gavage route was not successful; the study was stopped early because of anaphylaxis events that occurred in control and drug exposed animals. These events were likely due to the solubilizing agents[1] used in this study. A second 3-month study was successfully conducted in dogs using the fidaxomicin tablets in gelatin capsules (no solubilizing agent). In the second 3-month dog toxicity study no significant toxicity was noted; sporadic vomiting was noted, but was not occurring at a level that would raise concerns about the amount of drug received. Studies in rats and cynomologous monkeys also did not reveal significant toxicities. Fidaxomicin is labeled as Pregnancy category B.

Clinical Microbiology

The Clinical Microbiology assessment of fidaxomicin is discussed in Dr. Marsik's Clinical Microbiology review. He notes that data has been provided that demonstrates the activity of fidaxomicin against *Clostridium difficile* both in vitro and in vivo. Fidaxomicin acts against *C. difficile* through inhibition of RNA synthesis by bacterial RNA polymerase. Both in the laboratory and in a clinical isolate in the setting of recurrence, *C. diff* with decreased

[1] The solubilizing agent/vehicle used in this study was 9% labfrac WL1349, 24.3% labrasol, 13.6% labrafil M1944-CS, 33% Tween 80, 10% plurol oleique CC947, and 10% water.

susceptibility has been identified. In order to follow for the development of resistance in the postmarketing period, the approval includes a postmarketing commitment to monitor for resistance development for a five year period, reporting results annually.

Clinical Pharmacology

The clinical pharmacology of fidaxomicin is discussed in Dr. Kim's Clinical Pharmacology Review. She finds that the material in the NDA is acceptable from a clinical pharmacology perspective. The dose for fidaxomicin is 200mg orally twice daily for 10 days. Following oral administration, fidaxomicin and its major metabolite OP-1118 remain largely within the gastrointestinal tract. The major fidaxomicin metabolite, OP-1118 is formed via hydrolysis and this metabolite is active, but in comparison to the fidaxomicin, the parent drug, it is 32-fold less active. Mean fidaxomicin concentrations during the Tmax window (1-5 hours post dose) in plasma following oral administration were 22 ng/mL on Day 1 and 27 ng/mL at End of Therapy in patients in phase 3 trials. Mean OP-1118 concentrations in plasma during the Tmax window were 44 ng/mL on Day 1 and 79 ng/mL at End of Therapy. The range of measured concentrations (minimum and maximum concentrations observed) at the Tmax window in the population of patients from the phase 3 trials for whom samples were taken was wide for both fidaxomicin and OP-1118. No clinically significant effect was seen when fidaxomicin was taken with food and therefore it can be taken with or without food. No dosage adjustment is recommended for age, gender, or renal impairment. The effect of hepatic impairment has not been studied, but hepatic impairment is not expected to impact upon the elimination of fidaxomicin. No dose adjustment is recommended in the setting of co-administration with substrates of CYP enzymes. While there were increases in plasma levels of fidaxomicin when co-administered with a P-gp inhibitor, the available information supports that fidaxomicin may be administered with P-gp inhibitors. No dosage adjustment is needed for co-administration with P-gp substrates.

The Applicant conducted a phase 2 trial of fidaxomicin at doses of 50 mg, 100 mg, and 200 mg orally every 12 hours. The clinical cure rates by dose groups were, 50 mg 12/16 (75%); 100 mg 13/16 (81.3%); and 200 mg 15/15 (100%). The apparent dose-response supported the selection of the 200 mg orally twice daily dose regimen for the phase 3 program.

A thorough QT study was not conducted because of solubility limitations of fidaxomicin, the limited systemic absorption of fidaxomicin, and the lack of significant food effect so that it was not feasible to achieve plasma concentrations in healthy normal patients that would approximate or exceed those achieved in patients. Data from the phase 3 trials was examined and did not reveal a relationship between increasing fidaxomicin or OP-1118 concentrations and increasing QTcF interval.

Clinical Efficacy and Safety

The results of the clinical trials evaluating the safety and efficacy of fidaxomicin are discussed in detail in Dr. Iarikov's Clinical Review, Dr. Izem's Statistical Review, Dr. Alexander's

CDTL review and Dr. Laessig's Deputy Division Director's Review. The reader is referred to their reviews for a detailed discussion of safety and efficacy. The Applicant performed two randomized, double-blind, active controlled clinical trials comparing fidaxomicin 200mg orally twice daily for 10 days to vancomycin 125 mg orally twice daily for 10 days. The trials were designed to show non-inferiority of fidaxomicin to vancomycin on clinical response to therapy at the end of therapy visit. A justification supporting a non-inferiority margin of 10% has been provided. An additional endpoint evaluated for efficacy was sustained response at follow-up, 25 days after completion of therapy. The results for efficacy for the two trials are provided in Table 1.

Table 1. Clinical Response at End of Therapy and Sustained Response at 25-days Post Therapy (mITT population)

	Fidaxomicin % (N)	**Vancomycin % (N)**	**Difference (95% CI)**
Clinical Response at End of Therapy			
Study 003	88% (N=289)	86% (N=307)	2.6% (-2.9%, 8.0%)
Study 004	87% (N=253)	87% (N=256)	1.0% (-4.8%, 6.8%)
Sustained Response at 25-days Post Therapy			
Study 003	70% (N=289)	57% (N=307)	12.7% (4.4%, 20.9%)
Study 004	72% (N=253)	57% (N=256)	14.6% (5.8%, 23.3)

The trials demonstrate non-inferiority of fidaxomicin to vancomycin at the end of therapy. A greater proportion of fidaxomicin-treated patients had a sustained response at the 25-day post therapy visit. The trials demonstrate the efficacy of fidaxomicin in the treatment of CDAD.

The safety of fidaxomicin was evaluated in 676 subjects who received at least one dose of fidaxomicin including 564 subjects who received at least one dose of fidaxomicin in phase 3 trials. The number of deaths in the phase 3 trials were similar across treatment arms (6.4% fidaxomicin and 6.5% for vancomycin). Evaluation of the adverse events (AEs) in patients that died did not reveal a pattern of particular AEs suspected to be drug-related adverse events associated with death in either arm. There were 5 deaths in the fidaxomicin arm and 4 deaths in the vancomcyin arm that upon review were suspected to represent lack of efficacy; the events were similar across treatment arms. In the phase 3 trials 25.7% of fidaxomicin-treated patients and 23.2% of vancomycin-treated experienced serious adverse events. The adverse events of GI bleed (fidaxomicin 3.5%; vancomycin 1.7%) and decreased WBC counts (fidaxomicin 4.1%; vancomycin 1.7%) were carefully evaluated given the disproportionate rates by treatment arm. Evaluation of these events did not reveal a consistent pattern to further explain the events and their possible relationship to study therapy. In addition, the clinical pharmacology review performed analyses to explore whether there was a concentration relationship with fidaxomicin or its main fidaxomicin metabolite, OP-1118, and

GI bleed or decreased WBC count; the analysis did not find a relationship of concentration with these adverse events. The product labeling contains information on adverse events involving the gastrointestinal system and blood and lymphatic system. Treatment failures were reported in 2.3% of fidaxomicin-treated patients and 0.9% of vancomycin-treated patients. There were 3 cases of megacolon in fidaxomicin treated patients. The rates of these events and their small numbers were discussed at the Anti-Infectives Advisory Committee; given the small numbers, conclusions whether these events were related to study therapy or underlying disease condition could not be made. The most common adverse events were nausea (fidaxomicin 11%; vancomycin 11%), vomiting (fidaxomicin 7%; vancomycin 6%), and abdominal pain (fidaxomicin 6%; vancomycin 4%). Vomiting was the most common reason for study medication discontinuation; study medication discontinuations due to vomiting occurred at a rate of 0.5% for both fidaxomicin and vancomycin.

The evidence supports that the benefits of fidaxomicin for the treatment of CDAD outweigh the risks of fidaxomicin.

DMEPA / DDMAC / DSI Inspections / Pediatrics

DMEPA has consulted on the proprietary name and found it to be acceptable. The division met with DDMAC to discuss their recommendations and the product labeling.

The Division of Scientific Investigations performed clinical inspections and found that the data collected in support of the application appear to be reliable.

The pediatric study requirement for ages 0 to less than 6 months is being waived because necessary studies are impossible or highly impractical since the disease does not occur in this population. Pediatric studies for ages 6 months to less than18 years are deferred because the product is ready for approval for use in adults and the pediatric studies have not been completed. The approval includes requirements to conduct the deferred pediatric studies for ages 6 months to less than 18 years.

Advisory Committee

The fidaxomicin NDA was presented to the Anti-Infective Drugs Advisory Committee on April 5, 2011. On the question of whether safety and effectiveness had been demonstrated for fidaxomicin the committee voted 13 Yes; 0 No; 0 Abstain. The Committee discussed the gastrointestinal bleeding adverse events, leukopenia adverse events, and testing methodologies to diagnose CDAD. On the second question on the clinical significance of the lower recurrence rate at Day 31, the Committee vote was 6 Yes; 6 No; abstain 1. In the discussion that followed the vote, it was apparent the Committee Members felt that the sustained cure rate at Day 31 was of note, but that it was important to describe this as disease that remained resolved or as sustained cure and that the terms “global cure” and “recurrence” were either unfamiliar terms or somewhat different issues.

Postmarketing Study Requirements and Commitments

In addition to required pediatric studies, the approval also includes a Postmarketing Requirement to perform a study to evaluate the susceptibility of *C. difficile* to fidaxomicin over the first five years, reporting annually. There are also commitments to perform a clinical trial to evaluate safety and efficacy of fidaxomicin in patients with multiple recurrences of CDAD. This study will provide an opportunity to characterize efficacy in this population and also an opportunity to characterize safety in persons with multiple recurrences of CDAD. In addition there is a PMC to include a test for (b) (4) fidaxomicin in the drug substance specification.

Summary

I concur with the assessment of the review team that substantial evidence of safety and efficacy has been provided for fidaxomicin for the indication of treatment of *Clostridium difficile*-associated diarrhea in adults (age ≥18 years) and that the benefits of fidaxomicin outweigh the risks. This conclusion is also in concordance with the recommendation from the Anti-Infective Drugs Advisory Committee. The product labeling provides information describing the benefits and risks of fidaxomicin treatment for CDAD.

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/s/

EDWARD M COX
05/27/2011