CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 05-25-11

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective Products

SUBJECT: Deputy Division Director's Summary Review Memo for NDA 201-699, fidaxomicin 200 mg tablets (Tradename DIFICID™)

1.0 Background

Fidaxomicin, a new molecular entity, is a macrolide antibiotic with an 18-membered macrocyclic ester structure. Its mechanism of action is via inhibition of bacterial ribonucleic (RNA) polymerase. It is obtained from the fermentation of *Dactylosporangium aurantiacum* and belongs to a group of compounds known as the Tiacumicins. Fidaxomicin has a narrow in vitro spectrum of activity and is primarily active against vegetative *Clostridium* spp., such as *Clostridium difficile* (henceforth referred to as C diff).

C diff produces two exotoxins, toxin A and toxin B, and is a common cause of antibacterial-associated diarrhea. The mechanism by which these toxins cause diarrhea has not been fully elucidated; however, they appear to be cytotoxins. The presence of either toxin appears to be sufficient to cause diarrheal disease. While C diff disease acquisition is primarily associated with hospitalization, community-acquired disease is on the upswing. In addition to diarrhea, C diff infection may result in pseudomembranous colitis, toxic megacolon, colonic perforation, sepsis, and rarely, death. There is only one FDA approved antibacterial drug for the treatment of C diff-associated diarrhea (CDAD), which is oral vancomycin.

The applicant, Optimer Pharmaceuticals, Inc., has submitted NDA 201-699 in support of fidaxomicin 200 mg tablets and proposed a dose regimen of 200 mg po bid for 10 days. The requested indication is treatment of C diff infection and the prevention of recurrences. The submission contains the data and results from two Phase 3 trials for the requested indication, as well as additional clinical pharmacology and Phase 2 trials. This memo will summarize elements of all reviews by discipline; for detailed discussions, please refer to the respective chemistry, manufacturing, and controls (CMC), pharmacology/toxicology, microbiology, clinical, and biometrics reviews, and related consults.

2.0 Chemistry, Manufacturing and Controls

This application is recommended for approval by the CMC reviewer, Balajee Shanmugam, Ph.D. He concludes that the applicant has provided sufficient/adequate information to assure the identity, strength, purity, and quality of the drug product. The drug substance has been well-characterized and the manufacturing process is well documented. The impurities are qualified by toxicological studies and the acceptance criteria for some of the quality attributes have been successfully established. The manufacturing site has received an acceptable recommendation from the Office of Compliance.

The drug product is formulated as an immediate release tablet containing 200 mg of fidaxomicin. The tablets are white to off-white, film-coated, oblong-shaped and are debossed with "FDX" on one side and "200" on the other side. The manufacture of the product involves (b) (4) (b) (4) The drug product stability data provided for the 200 mg dosage strength supports the requested expiry of 24 months when stored at 20°-25°C. The dissolution data have been reviewed by Dr. Elsbeth Chikhale and found to be adequate.

The drug substance occurs as a white to off-white powder and is poorly soluble in water. Fidaxomicin has poor solubility, poor permeability, and absorption. It is produced by fermentation as noted above, (b) (4) (b) (4) The three registration batches will remain on long-term stability for a minimum of 48 months.

For a Phase 4 post-marketing commitment per the Agency's recommendation, the company has agreed to include a test for (b) (4) in the drug substance specification by submitting a supplement (CBE-0) within 6 months of approval of the application.

3.0 Summary of Pharmacology/Toxicology

Based on the review of the nonclinical pharmacology and toxicology information by Dr. Amy Nostrandt, this application is recommended for approval. Drs. Wendelyn Schmidt and Abigail Jacobs have provided concurrence. Key findings from her review include: 1) cardiologic effects were minimal as tested in the hERG assay, telemeterized dogs (single 1 mg/kg intravenous dose), and in oral dog and monkey pharmacology studies; 2) no other respiratory, CNS, or renal toxicities were identified in the safety pharmacology or general toxicology

studies; 3) absorption was variable and low by the oral route in most species tested; 4) metabolism by gut and intestinal enzymes in rats and dogs included products formed by humans and excretion was primarily by the fecal route; 5) in dogs, less than 1% of the dose was excreted by the urine.

In addition, toxicity studies of up to 3 months duration have been conducted by the oral and intravenous routes in rats, dogs, and cynomolgus monkeys. All studies were conducted at the maximum feasible dose, but due to variable absorption, low solubility, and presumed low bioavailability, studies by routes other than the oral route were requested to better define the toxic potential of fidaxomicin. The initial one month oral gavage studies in rats and monkeys with labrasol as a vehicle showed minimal toxicities at the maximum feasible dose of 90 mg/kg. Solubility issues prevented use of doses higher than 90 mg/kg. Intravenous studies in rats for 14 days with three different vehicles were conducted. Different vehicles were used to increase solubility. No fidaxomicin-related toxicities were noted at the maximum feasible doses (<4 mg/kg as an i.v. bolus). A three month oral capsule study in the dog showed no toxicity at the maximum feasible dose of approximately 1 g/kg/d.

Segment I and II reproductive toxicity studies were conducted in rats and rabbits. Fidaxomicin had no effects on fertility or development through implantation in the rat at i.v. doses in 1% sotulol HS15 of up to 6.3 mg/kg. In the rat by the i.v. route in 1% sotulol HS15, when administered during the period of organogenesis, fidaxomicin had no effect on maternal or fetal parameters at the highest dose tested, 12.6 mg/kg. In the rabbit, the highest dose tested, 7.0 mg/kg, was a NOAEL for both dams and offspring. Dr. Nostrandt concurs with the applicant that the pregnancy category should be B.

Fidaxomicin and its main metabolite, OP-1118, were negative for genotoxicity in the Ames bacterial assay. In the chromosomal aberration assay, fidaxomicin was positive, while OP-1118 was negative. Fidaxomicin was also negative in the rat micronucleus assay.

4.0 Summary of Clinical Pharmacology

The applicant conducted ten *in vitro* studies evaluating metabolism by human intestinal/liver microsomes and hepatocytes, inhibition/induction of cytochrome P450 (CYP) isoenzymes, and efflux/inhibition of P-glycoprotein (P-gp), six Phase 1 studies assessing the pharmacokinetics of fidaxomicin and its major active metabolite including single ascending dose and multiple ascending dose, effect of food, and drug-drug interaction (DDI) studies via intestinal P-gp or CYP enzymes, one supportive Phase 2 study evaluating the safety and effectiveness of various doses in the treatment of CDAD (50, 100, and 200 mg po bid for 10 days), as well as the two Phase 3 studies. The clinical pharmacology data was reviewed by Dr. Aryun Kim and found to be acceptable from her perspective.

The recommended dose is 200 mg po bid for 10 days. Some of the key points from the clinical pharmacology review include:

- A clear dose response relationship was evident from the supportive Phase 2 safety and effectiveness trial as efficacy was greatest with the 200 mg dose for the outcomes of clinical cure, symptom relief, and time to resolution of diarrhea while there was no discernable dose-dependent trend for any safety parameters.
- Systemic absorption of fidaxomicin is minimal following a p.o. dose in healthy adults, however is somewhat higher in patients although concentrations remain in the ng/mL range.
- *In vitro* studies with Caco-2 cells indicate fidaxomicin and OP-1118 are substrates of P-gp.
- No clinically significant effect was observed with food.
- Fidaxomicin is mainly confined to the GI tract following oral administration.
- *In vitro* studies with human intestinal and liver microsomes and hepatocytes indicate fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form the major active metabolite, OP-1118. CYP enzymes do not appear to play a major role in the metabolism of fidaxomicin or the formation of OP-1118.
- Fidaxomicin and OP-1118 are primarily excreted in the feces.
- In Phase 3 trials, peak concentrations of fidaxomicin and OP-1118 were approximately 2-4 times higher in the elderly ($\geq$65 years of age) compared to those < 65 years of age. Peak concentrations of fidaxomicin did not vary by gender. No dose adjustment is recommended based on renal impairment.
- In a DDI study of fidaxomicin coadministered with cyclosporine (P-gp inhibitor), plasma concentrations of fidaxomicin and OP-1118 were increased approximately 4-9 fold for Cmax and 2-4 fold for $AUC_{0\text{-inf}}$ although values remained in the ng/mL range. In Phase 3 trials, there was a trend towards lower efficacy and higher incidence of adverse events with P-gp inhibitor use, however results for the comparator vancomycin arm were similar. Fidaxomicin may be coadministered with P-gp inhibitors
- In a DDI study of fidaxomicin coadministered with digoxin (P-gp substrate), there was no effect on the PK of digoxin. No dose adjustment is recommended for coadministration with substrates of P-gp.
- In a DDI study with midazolam/warfarin/omeprazole (CYP3A4/2C9/2C19 substrates) coadministered with fidaxomicin, no significant effect was noted. No dose adjustment is recommended for coadministration with substrates of CYP enzymes.

Dr. Kim has no recommended Phase 4 commitments.

5.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Dr. Frederic Marsik, has recommended approval of this application, based on his review of the clinical microbiology data. He concludes that the applicant has demonstrated activity of fidaxomicin against C diff both in vitro and in vivo. He has recommended changes to the package insert that have been incorporated by the applicant, and has recommended a post-marketing requirement to monitor for the development of resistance to fidaxomicin, which will be incorporated into the action letter. Key findings from his review include:

- Fidaxomicin has a narrow spectrum of activity, being primarily active against vegetative *Clostridium* spp. It has reduced in vitro activity against *Enterobacteriaceae, Pseudomonas aeruginosa,* staphylococci, streptococci, *Hemophilus influenzae, Neisseria gonorrheae, Acinetobacter baumannii*, and *Candida albicans*. However it is active against the Gram-positive bacterium *Micrococcus luteus*.
- The MIC_{90} against vegetative C diff is 0.25 mcg/mL
- Fidaxomicin is bactericidal against C diff in vitro.
- The post-antibiotic effect of fidaxomicin and OP-1118 is in the range of 5 to 10 hours.
- In vitro studies indicate a low frequency of spontaneous decreased susceptibility of C diff to fidaxomicin. Serial passage studies confirm this. However, one C diff isolate with decreased susceptibility to fidaxomicin was created in the labs and isolated from one subject in the Phase 3 clinical trials who had a recurrence of CDAD after treatment with fidaxomicin. The isolate from the patient had the same mutation (VA1143Gly) in the beta subunit of RNA polymerase as the lab-derived C diff mutant. The MIC of the isolate from the patient was 0.06 mcg/mL prior to fidaxomicin treatment and 16 mcg/mL at the time of disease recurrence.
- No decreased susceptibility to rifampin, azithromycin, ampicillin, metronidazole, vancomycin, or clindamycin has been detected in C diff with decreased susceptibility to fidaxomicin
- No antagonism was noted between fidaxomicin and ampicillin, azithromycin, clindamycin, metronidazole, rifampicin, rifaximin, telithromycin, or vancomycin has been demonstrated in vitro. Synergism for both fidaxomicin and OP-1118 has been observed with the rifamycin class of compounds and marginally with ampicillin, clindamycin, and metronidazole.
- In vitro susceptibility testing of fidaxomicin against anaerobic bacteria can be done by anaerobic standardized methods.
- In vitro susceptibility test interpretive criteria have not been established because there was no correlation identified between clinical success and

MICs of fidaxomicin need to prevent the growth of C diff isolated from study subjects with CDAD.

- An in vitro MIC susceptibility quality control range was developed so that labs that wish to determine the MIC can do so.

6.0 Summary of Clinical Efficacy

Optimer submitted two identically designed Phase 3 trials that were randomized (1:1), double-blind, multicenter, active-controlled, noninferiority trials in CDAD patients. Study 003 enrolled subjects in the US and Canada, while study 004 enrolled subjects in Canada, the US, and Europe. Both trials compared 10 days of fidaxomicin 200 mg po bid to 10 days of vancomycin 125 mg po qid in subjects with CDAD. Randomization was stratified by prior CDAD episode with two strata: 1) no prior episode in the last 3 months or 2) a single prior episode in the last 3 months. Note that the applicant for the purposes of the study protocol (b) (4) has used the term C diff infection (CDI), however this implies the infection could be extra-intestinal, which is not what was studied. Historically, the Agency has used CDAD, as noted in the Vancocin capsule label, as well as in the Warnings section of other antibacterial product labeling. Therefore, the review team has agreed that CDAD should be used instead of CDI.

The applicant has provided justification for a 10% noninferiority margin for clinical cure at the end-of-treatment (EOT) visit. The statistical reviewer, with some modifications to the historical information used to evaluate the historical evidence of treatment effect, has concurred that a 10% NI margin can be justified for this endpoint.

As discussed above, the primary outcome was clinical cure at the EOT visit (Day 10-11) and was defined as subjects who required no further treatment for CDAD, had a frequency of unformed stools of 3 or fewer for two consecutive days, who had a marked reduction in the number of unformed bowel movements and who had residual mild abdominal discomfort, or in subjects who had a rectal collection device, had a decrease in the volume of diarrhea of 75%. Clinical failures were subjects who required additional CDAD therapy. The primary analysis population was the modified intent-to-treat (mITT) which included the group of randomized subjects with CDAD confirmed by > 3 unformed bowel movements in the 24 hours prior to randomization and a positive toxin assay who received at least one dose of study medication.

During the review of CRFs, the medical officer noted some subjects who were declared cures by the applicant who were not felt to be cures because they had either 1) died during the study, 2) received concomitant medication treating CDAD during the treatment period or follow-up, or 3) their recurrence assessment visit occurred before study day 31. The statistical reviewer and medical officer reclassified these subjects as failures. The results of the Agency's primary efficacy analysis are provided in Table 1.

Table 1: Clinical cure at EOT (mITT population)

	Fidaxomicin % (N)	**Vancomycin % (N)**	**Difference (95% CI)**
Study 003	88% (N=289)	86% (N=307)	3% (-2.9%, 8.0%)
Study 004	88% (N=253)	87% (N=256)	1% (-4.8%, 6.8%)

As the lower bound of the 95% confidence interval is greater than -10%, the two studies have demonstrated the noninferiority of fidaxomicin to vancomycin for the treatment of CDAD. Note that for the purposes of labeling, the term "clinical response" is used (b) (4) (b) (4) (b) (4)

In study 003, the Applicant had an exploratory analysis for the endpoint of Global Cure, which was defined as cure at EOT with no recurrence at follow-up, where no recurrence was the maintenance of a non-diarrheal state up to and through the post-study visit (25 days after EOT). In study 004, Global Cure was a key secondary endpoint. Table 2 shows the results of the Global Cure analyses for both studies.

Table 2: Global Cure (mITT population)

	Fidaxomicin N (%)	**Vancomycin N (%)**	**Difference [2] (95% CI)**
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 results of these analyses demonstrate the superiority of fidaxomicin over vancomycin for the endpoint of Global Cure. Note that for the purposes of labeling, the term "sustained clinical response" is used (b) (4)

The biometrics reviewer conducted additional sensitivity analyses, as well as analyses for the per protocol population, and while the point estimates and

confidence intervals changed somewhat for each analyses, they all support the Applicant's conclusion regarding the noninferiority of fidaxomicin to vancomycin for clinical cure at EOT, and superiority of fidaxomicin to vancomycin for the endpoint of clinical cure. A notable exception was for the subgroup of subjects who had the BI strain of C diff, for whom a benefit of fidaxomicin over vancomycin on Global Cure was not demonstrated.

In view of the findings of the efficacy analyses, the biometrics reviewer, Dr. Rima Izem, recommends approval of the application. The primary medical reviewer, Dr. Dmitri Iarikov, and the CDTL, Dr. John Alexander, concur with her recommendation.

7.0 Summary of Safety

Please refer to Dr. Dmitri Iarikov's review for additional details regarding the safety of fidaxomicin. The safety database for this NDA includes 676 subjects who received at least one dose of fidaxomicin in all studies, and 564 subjects who received at least one dose of fidaxomicin in the Phase 3 trials. The mean duration of exposure to fidaxomicin in the Phase 3 trials was 10.2 days.

There were 75 deaths including 74 in the Phase 3 trials and one in a Phase 2 trial. In the Phase 3 trials, the incidence of deaths was similar for both treatment arms (6.4% for fidaxomicin and 6.5% for vancomycin). The treatment-emergent adverse events (TEAEs) that resulted in death in the fidaxomicin arm that occurred most frequently were respiratory failure in four subjects, pneumonia and sepsis in three subjects. In the vancomycin group, the most frequently reported TEAEs resulting in death were sepsis in four subjects and multiorgan failure in three subjects. All of the TEAEs leading to death were assessed by the investigator as not related or unlikely to be related to study drug. Dr. Iarikov determined that five deaths in the fidaxomicin group and four in the vancomycin group could possibly be related due to lack of efficacy.

The incidence of serious adverse events in the Phase 3 trials was 25.7% for the fidaxomicin group and 23.2% for the vancomycin group. Adverse events of interest that occurred at a higher rate in the fidaxomicin group were GI hemorrhage, megacolon, and decrease in WBC count.

There were 20 (3.5%) fidaxomicin-treated vs. 12 (1.7%) vancomycin-treated subjects in the Phase 3 trials who experience an adverse event of GI bleed. However, review of the actual events revealed no particular consistent pattern, although lower GI bleeds were more frequent for the fidaxomicin group overall. Dr. Iarikov recommends postmarketing surveillance for this event.

There were more subjects in the fidaxomicin than in the vancomycin group with adverse events related to decreased WBC counts (4.1% vs. 1.7%). However, no abnormal shifts in hematology values were reported for subjects in the

fidaxomicin group, and there was no bone marrow toxicity noted in the animal toxicology studies. The majority of fidaxomicin treated subjects had underlying comorbidities or received concomitant meds that may have contributed to the decreased WBC count compared to the vancomycin treated subjects.

More subjects in the fidaxomicin group compared to the vancomycin group discontinued the study due to treatment failure (2.3% vs. 0.9%, respectively), and all three cases of megacolon were observed in fidaxomicin treated patients However, based on the small number of megacolon events and the similar clinical cure rates at EOT for both treatment groups, it is difficult to make conclusions regarding an association with fidaxomicin treatment and megacolon, particularly since megacolon is a well-recognized complication of CDAD.
The most common TEAEs in both the fidaxomicin and vancomycin groups were nausea (11.0% vs. 11.3%), vomiting (7.3% vs. 6.3%), hypokalemia (7.3% vs. 6.5%), headache (6.6% vs. 4.6%), abdominal pain (5.9% vs. 3.9%), diarrhea (5.0% vs. 6.7%), constipation (4.4% vs. 2.1%), and pyrexia (4.3% and 5.3%).

Drs. Iarikov and Alexander conclude that given the demonstrated efficacy of fidaxomicin for the treatment of CDAD, and the superiority compared to vancomycin for Global Cure, that the benefits of fidaxomicin outweigh the safety risks and that the application should be approved.

8.0 Summary of Other Regulatory Issues

The Division of Scientific Investigations conducted audits of four clinical investigators who enrolled subjects in either Phase 3 trial. The interim classification for three sites is VAI and NAI for the fourth site. The applicant was also inspected and received a final classification of VAI. DSI has concluded that none of the findings from the inspections of the clinical sites or the applicant are likely to significantly impact the reliability of the data.

OSE has reviewed the labeling, carton, and container labeling and provided comments that will be conveyed to the applicant. DMEPA has conducted a proprietary name, label, and labeling review and has no objection to the proposed proprietary name of Dificid.

(b) (4)

However, upon further review of the literature by Dr. John Alexander which described a C diff colonization rate of about 30% for patients aged 1 to < 6 months, and of about 40% for patients aged < 1 month, the Division has determined that study of the pediatric population < 6 months of age should be waived.

This application was presented at a meeting of the Anti-infective Drugs' Advisory Committee on April 5, 2011. The committee voted unanimously that the applicant had demonstrated the efficacy and safety of fidaxomicin for the treatment of CDAD. Important points of discussion included the fact that very few of studied subjects had prior episodes of CDAD, which should be noted in the label and considered for a PMC. (b) (4) (b) (4) (b) (4) Taking these comments into account and for the purposes of labeling, the review team has decided to use the terms clinical response to reflect the outcome at EOT and sustained clinical response at 25 days post-therapy to reflect the outcome (b) (4)

The following PMRs and PMCs have been agreed to by the applicant and will be included in the action letter:

PMRs

Conduct a prospective clinical trial of 10 days of Dificid (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 Dificid (fidaxomicin).

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.

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.

PMCs

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.

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

9.0 Recommendation

I concur with the findings and conclusions of the review team that the applicant has demonstrated substantial evidence of the efficacy and safety of fidaxomicin

for the treatment of CDAD. With respect to the additional claim that the applicant has requested of "reduction in recurrence", we have determined that it is not appropriate to include this (b) (4) Also, not all fidaxomicin-treated subjects were recurrence-free. However, since the finding of superiority to vancomycin for sustained clinical response was demonstrated and replicated in the two Phase 3 trials, this outcome will be reflected in the Description of Clinical Studies section of the package insert. Since there is only one FDA approved product for the treatment of CDAD, the availability of a new therapeutic option is important for patients and providers alike. Therefore, I recommend approval of this application.

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
05/25/2011