CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201,699
Applicant	Optimer Pharmaceuticals, Inc.
Date of Submission	November 30, 2010
PDUFA Goal Date	May 30, 2011
Proprietary Name / Established (USAN) names	Dificid™ / fidaxomicin
Dosage forms / Strength	200 mg Tablets
Proposed Indication	1. Treatment of *Clostridium difficile*-associated diarrhea and reducing the rate of recurrent *C. difficile* infection
Recommended:	Approval

1. Introduction

Optimer Pharmaceuticals, Inc. submitted a NDA for fidaxomicin 200-mg tablets for the treatment of patients with *Clostridium difficile*-associated diarrhea (CDAD). This application was a rolling NDA submission; the final portion was received on November 30, 2011. The proposed indication is based on the results of two pivotal, randomized, double-blind, non-inferiority trials comparing fidaxomicin to vancomycin for the treatment of CDAD. The application was made a priority review on the basis of results showing that fewer fidaxomicin patients had recurrence of CDAD during the follow-up period. This CDTL review will summarize the findings of the various discipline reviews.

2. Background

The drug development program for fidaxomicin was conducted under an investigational new drug (IND) application. IND 64,435 for OPT-80 (aka fidaxomicin and PAR-101) was submitted in August 2003. Fidaxomicin was selected for development based on in vitro activity against *C. difficile* and low systemic absorption in animals, suggesting it would work locally in the GI tract. The product was given a fast track designation for treatment of CDAD in October 2003 on the basis of the limited treatment options available for CDAD; the designation noted the risk of relapse with currently existing therapies as one of the limitations of existing treatment. Some issues that were addressed under the IND are pertinent to the NDA application. The low solubility and absorption of fidaxomicin made it difficult to evaluate potential toxicities of the drug in animal toxicology studies. Because of the low absorption of fidaxomicin in CDAD patients, and the even lower absorption in healthy adults, a meaningful thorough QTc study was not considered to be feasible. Based on available in vitro/animal data and the low systemic exposures in humans, the potential for adverse QTc effects is considered extremely unlikely. The thorough QTc study was waived for this product.

The pivotal trials submitted in the NDA application were conducted between 2006 and 2009 under the IND. The non-inferiority design was discussed prior to beginning the trial. Limited evidence from a small placebo-controlled study provided the basis for the protocol design. After the trials began, additional results from contemporary trials have provided greater support for the NI margin.

3. Chemistry/Manufacturing Controls

The reader is referred to the Chemistry review by Dr. Balajee Shanmugam for details of the CMC review. Dr. Shanmugam concluded that the NDA continued adequate information to assure the identity, strength, purity and quality of the drug product. The CMC reviewer recommended approval of the NDA. A separate CMC Biopharmaceutics review was conducted by Dr. Elsbeth Chikhale to evaluate dissolution data in the application. The dissolution specifications were accepted, and the data supported the over-encapsulation of the drug product and the comparator (Vancocin) for blinding in the pivotal trials. Dissolution data did not support the equivalence of an old formulation used in the clinical trials with the to-be-marketed formulation, though the data for the old formulation still provided useful information to support the new formulation.

- General product quality considerations

The drug substance, fidaxomicin, is a new molecular entity produced by fermentation from *Dactylosporangium aurantiacum*, an actinomycete. The drug substance is obtained through a process of (b) (4) The drug substance exists in different forms (b) (4) Fidaxomicin is a low solubility and low permeability (BCS Class 4) compound, which are desirable characteristics for an active ingredient intended to act locally within the GI tract.

The drug product is formulated as immediate release tablets containing 200 mg of fidaxomicin. The tablets are white to off-white, oblong, film-coated, and debossed with 'FDX' on one side and '200' on the other. The manufacturing process for the drug product involves (b) (4) Sufficient stability data were provided to support the requested 24-month shelf-life when stored at 20 to 25°C.

- Facilities review/inspection

Per the CMC review, all facilities identified in the NDA have been recommended as Acceptable by the Office of Compliance.

- Other notable issues

There was disagreement with the applicant regarding the pharmacological classification of fidaxomicin. In the NDA submission, the applicant proposed that the pharmacological classification should be as a (b) (4) although Optimer had identified fidaxomicin as a

macrolide in the IND submission. Based on chemical structure, fidaxomicin was considered by the CMC review team to belong to the macrolide class. (b) (4) (b) (4) (b) (4) (b) (4) .

The CMC review indicates that the applicant has committed to include a test for the (b) (4) (b) (4) in the drug substance specification by submitting a CMC supplement within 6 months of approval of the application. The applicant is currently attempting to validate an (b spectroscopy test for identity of (b) (4) in the drug substance specification. The applicant) agreed to maintain an (b) (4) until the validation of the new test method can be completed.

4. Nonclinical Pharmacology/Toxicology

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The reader is referred to the pharmacology/toxicology (P/T) review by Dr. Wendelyn Schmidt for detailed information. The reviewer recommended approval from the P/T perspective. As noted previously, fidaxomicin absorption was variable and low by the oral route in animals. In dogs, less than 1% of the dose was excreted in urine. Toxicity studies (oral and IV) were conducted in rats, dogs, and cynomolgus monkeys. Oral studies showed minimal toxicity at the maximum feasible doses (90 mg/kg) in rats and monkeys. An oral, 3-month study in dogs receiving up to 1 g/kg/day (maximum feasible) showed no toxicity. Intravenous studies in rats were conducted with three different vehicles, but no fidaxomicin-related toxicities were identified at maximum feasible doses (<4 mg/kg IV bolus). Metabolism within the intestines in rats and dogs included the metabolites of fidaxomicin seen in humans; the main human metabolite was OP-1118.

- Carcinogenicity

Long-term carcinogenicity studies have not been conducted with fidaxomicin, since the duration of drug use is less than 2 weeks. Neither fidaxomicin nor OP-1118 was mutagenic in the Ames assay. Fidaxomicin and OP-1118 were clastogenic in Chinese hamster ovary cells. Fidaxomicin was negative in the rat micronucleus assay.

- Reproductive toxicology

Reproductive toxicology studies were conducted in rats and rabbits. No reproductive effects were noted in these studies at the highest doses tested, given by IV. The plasma exposures were approximately 200- and 66-fold that in humans, in rats and rabbits, respectively.

- Other notable issues

No cardiac effects of fidaxomicin were noted from the HERG assay or studies in telemetrized dogs.

Low and variable absorption in animal species tested led to requests for animal toxicology studies by the IV route; since it was not clear whether humans with CDAD could be exposed to higher systemic concentrations due to increased intestinal permeability. The poor solubility of fidaxomicin also made difficult the interpretation of IV toxicology studies, since control animals also showed toxic effects from the vehicle used for solubilization. Ultimately, a 3-month oral study in dogs using a gelatin capsule formulation was considered the definitive study for toxicity.

5. Clinical Pharmacology/Biopharmaceutics

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The reader is referred to the Clinical Pharmacology review by Dr. Aryun Kim for detailed information. The review stated that the application was acceptable from the clinical pharmacology perspective. As noted previously, fidaxomicin is mainly confined to the gastrointestinal tract. Fidaxomicin is hydrolyzed to form the major metabolite, OP-1118 in the intestines. CYP enzymes do not appear to play a role in the metabolism of fidaxomicin. In healthy adults following a single 200-mg dose, the C_{max} was 5.2±2.8 ng/mL and 12±6.1 ng/mL for fidaxomicin and OP-1118, respectively. Concentrations of fidaxomicin and OP-1118 in patients given 200 mg of fidaxomicin twice daily for 10 days were somewhat higher than concentrations in healthy adults, but were still in the nanogram/mL range. Mean concentrations at 1-5 hours on Day 1 in phase 3 patients were 22.4 ng/mL and 43.6 ng/mL for fidaxomicin and OP-1118, respectively. At end of therapy, the mean concentrations were 26.7 ng/mL and 79.1 ng/mL for fidaxomicin and OP-1118, respectively. There was no significant effect of food on systemic exposures of fidaxomicin and OP-1118. The ranges of concentrations of fidaxomicin and OP-1118 in feces were reported as 639-2710 mcg/g and 213-1210 mcg/g, respectively.

- Drug-drug interactions

Drug-drug interaction studies were conducted to evaluate potential interactions with CYP substrates and P-glycoprotein (P-gp) inhibitors and substrates. Co-administration of fidaxomicin with a cocktail of midazolam, warfarin, and omeprazole (CYP3A4, CYP2C9, and CYP2C19 substrates) had no significant effects on the substrates. No dosage adjustment was recommended for co-administration with CYP substrates. Co-administration of fidaxomicin with digoxin (a P-gp substrate) showed no significant effects on the pharmacokinetics of digoxin. No dosage adjustment was recommended for co-administration with P-gp substrates.

Co-administration of fidaxomicin with cyclosporine (a P-gp inhibitor) resulted in increased plasma concentrations of fidaxomicin and OP-1118. C_{max} increased 4-9 fold and AUC_{0-inf} increased 2-4 fold for these compounds. In phase 3 trials, a trend toward lower efficacy and more adverse events were seen in fidaxomicin-treated patients who also received P-gp inhibitors; however, the same trends were seen in vancomycin-treated patients. Based on these findings, it did not appear that co-administration of fidaxomicin with P-gp inhibitors

significantly altered the safety profile or efficacy of fidaxomicin. Although systemic exposure to fidaxomicin and OP-1118 is increased by concomitant administration of Dificid with P-gp inhibitors, no dosage adjustment is recommended.

- Pathway of elimination

Fidaxomicin and OP-1118 are mainly excreted in feces. In healthy adults (n=11) receiving a single dose of fidaxomicin, 26.4% of the dose was recovered as fidaxomicin in stool and 66.2% was recovered as OP-1118 in stool. In another study of healthy adults, less than 1% of a single dose was recovered in urine as OP-1118 only.

- Intrinsic factors

Intrinsic factors were evaluated in fidaxomicin-treated patients from large comparative trials, using peak plasma concentrations within a 1-5 hour T_{max} window. These peak concentrations did not vary by gender. No trends were identified for differences in peak concentrations by varying degrees of renal impairment. Renal impairment is not expected to significantly alter the pharmacokinetics for this drug product. Elderly patients (≥65 years of age) had peak concentrations of fidaxomicin and OP-1118 that were approximately 2-4 times higher than concentrations in non-elderly patients. Fidaxomicin-treated elderly patients were noted with lower clinical response rates and more adverse events compared to non-elderly patients; however, similar trends were seen in vancomycin-treated elderly patients. No dosage adjustment was recommended for any of these intrinsic factors.

- Demographic interactions/special populations

Findings in elderly patients were discussed with intrinsic factors above. Fidaxomicin has not been studied in pediatric patients. The clinical trials submitted in the NDA have only included adults (>18 years of age). There were no notable demographic interactions identified.

- QT assessment

No thorough QT study was performed for this drug product. Because of limited solubility of the product, minimal systemic absorption in healthy adults, lack of food effect, and higher concentrations reported in CDAD patients; any TQT study in healthy adults was not going to be considered informative about the risk of QT prolongation in CDAD patients. It is not possible to conduct a study where healthy adults would have higher systemic exposures than those seen in CDAD patients. The review team agreed that a thorough QT study should not be conducted, because it would not be informative. The clinical QT assessment was based on pooled data from the phase 3 trials. Increased concentrations of fidaxomicin and OP-1118 were not associated with increases in QTcF.

- Other notable issues

There was some suggestion of an exposure response relationship for efficacy from a phase 2 open-label, dose-ranging trial in CDAD patients. The trial included 47 patients who were

randomized to receive 50 mg, 100 mg, or 200 mg of fidaxomicin every 12 hours for 10 days. In this trial, clinical response was reported in 12/16 (75%) patients in the 50 mg group, 13/16 (81%) patients in the 100 mg group, and 15/15 patients in the 200 mg group. This was the basis for the dose regimen (200 mg every 12 hours) used in phase 3 trials. There was no relationship seen between dose and reported adverse events in this small trial.

6. Clinical Microbiology

- General considerations

Fidaxomicin has demonstrated in vitro activity against *C. difficile*; studies showed a MIC_{50} and MIC_{90} of 0.25 mcg/mL (range 0.12-0.25). In vitro activity was also seen for *Clostridium perfringens* and *Micrococcus luteus*, but this activity is not relevant to the proposed claim. There was reduced activity against Enterobacteriaceae, staphylococci, streptococci, *Acinetobacter baumanii*, and *Candida albicans* relative to fidaxomicin activity against *Clostridium* spp. The activity of OP-1118 was 1/32 that of the parent compound against *C. difficile*. The mechanism of action for fidaxomicin is by inhibition of RNA synthesis by RNA bacterial polymerase, interfering with transcription initiation. Fidaxomicin acts at a different site than the rifamycins. Laboratory studies showed a low propensity for development of bacterial resistance, but a *C. difficile* mutant with decreased susceptibility was generated. This isolate had a single mutation of the beta subunit of RNA polymerase.

In clinical trials, susceptibility interpretive criteria could not be established. There was no correlation noted between clinical success and MIC for baseline isolates of *C. difficile*. However, one patient treated with fidaxomicin in clinical trials developed a recurrence of CDAD and had a *C. difficile* isolate with an MIC of 16 mcg/mL. This MIC was higher than the MIC (0.06 mcg/mL) for baseline isolate from this patient. This isolate was found to contain a single mutation (Val-1143-Gly) in the beta subunit of RNA polymerase. The same mutation occurred during in vitro resistance studies with a different isolate of *C. difficile*.

- Discussion of primary and secondary reviewers' comments and conclusions

The clinical microbiology review was conducted by Frederic J Marsik, Ph.D., the clinical microbiology team leader. Dr. Marsik recommended approval from the clinical microbiology perspective.

- Other notable issues

Susceptibility interpretive criteria could not be established for fidaxomicin, but methods for MIC determination (including quality control) were developed. The clinical microbiology reviewer has recommended surveillance studies to monitor changes in *C. difficile* susceptibility to fidaxomicin over time.

7. Clinical/Statistical - Efficacy

The statistical review of the NDA application was conducted by Dr. Rima Izem, and the clinical review was conducted by Dr. Dmitri Iarikov. The reader is referred to these reviews for detailed information about the efficacy determination for fidaxomicin. Both reviewers recommended approval, concluding that the efficacy of fidaxomicin was demonstrated in the pivotal trials.

The evaluation of efficacy is based on the results of two randomized, double-blind, multicenter, non-inferiority trials comparing fidaxomicin (200 mg twice daily for 10 days) to vancomycin (125 mg four times daily for 10 days). These two trials were identical in design. The first trial (Trial 003) was conducted in the US and Canada in 2006-2008. The second trial was conducted in the US, Canada, and the EU in 2007-2009. The trials enrolled adult patients meeting baseline criteria for CDAD. Patients were stratified based on whether they had no prior history of CDAD, or an episode of CDAD within the 3 months prior to enrollment. There were no significant differences in demographic factors or baseline characteristics between treatment arms identified in either of the clinical trials.

The primary endpoint for the clinical trials was evaluation of clinical response at the end of therapy visit (Day 10 ± 2). The clinical response was based on the investigator's judgment that baseline symptoms had improved sufficiently such that additional CDAD treatment was not needed. The non-inferiority margin of 10% for this clinical trial was supported by recent clinical trials showing superiority of vancomycin to tolevamer (see appendix A of the statistical review). For the primary endpoint, the clinical cure rates were 88% for the fidaxomicin arm and 86% for the vancomycin arm in trial 003. In trial 004, the clinical cure rates were 88% for the fidaxomicin arm and 87% for the vancomycin arm. The 95% confidence intervals for the differences in cure rates (fidaxomicin - vancomycin) were (-2.9%, 8.0%) for trial 003 and (-4.8%, 6.8%) for trial 004.

Global cure rate (b) (4) was also evaluated in both trials. It is recognized that there is a high rate of recurrent CDAD infection after successful treatment. The applicant (b) (4)

The applicant evaluated CDAD recurrence among patients who were considered cured on the primary endpoint. To evaluate recurrence, the applicant planned contact by phone or in person out to day 36 of the trial. The applicant's evaluation of recurrence relied on proven CDAD recurrence based on a positive toxin assay on diarrheal stool samples at the time of recurrence. While this could be viewed as a conservative analysis is some respects, there were several issues with the applicant's analysis that were addressed in several sensitivity analyses conducted by the reviewers. The sensitivity analysis (b) (4) evaluated suspected recurrences based on presence of diarrhea and CDAD treatment, regardless of toxin assay results. Patients who died during the follow-up period were also considered failures in the sensitivity analysis. Finally, a multiple-imputation method was used to assign outcome values for patients who were considered cured in the primary analysis, but had missing information for follow-up assessments. For the sensitivity analysis, patients were considered to have complete information for assessment of outcome if they were followed for at least 21 days

after the end of treatment. The sensitivity analysis results for sustained clinical response through 21 days after the end of treatment are provided in the table below from the statistical review.

Study	003		004	
Global Cure Rate Sensitivity 2	fidaxomicin 71%	vancomycin 57%	fidaxomicin 72%	vancomycin 59%
Difference[1] 95% CI[2]	13.1% (5.0% , 21.2%)		13.3% (4.5%, 22.0%)	
Percent Total Variability Due to Missingness[3]	2.8%		4.1%	

From Statistical Review – Table 15, page 28

1. Difference = Global Cure Rate fidaxomicin arm – vancomycin arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio (1+1/25)*B/ V, where V = W + (1+1/25)*B, B is the between imputed samples variation and W is the within imputed samples variation.

The statistical reviewer also provided the results of a modified sensitivity analysis. The only difference for this analysis was that the follow-up period was defined as 25 days after the end of treatment, rather than 21 days. This resulted in roughly 2 percent more of patients in each group having a 'missing' outcome that was imputed. The results are shown in the table below and were used as the basis for labeling of sustained clinical response in the Clinical Studies section of the package insert.

Trial	003		004	
Sustained Clinical Response	fidaxomicin 70% (N=289)	vancomycin 57% (N=307)	fidaxomicin 72% (N=253)	vancomycin 57% (N=256)
Difference 95% CI	12.7% (4.4%, 20.9%)		14.6% (5.8%, 23.3%)	

Analyses were performed to evaluate the differences in outcomes in multiple subgroups of interest. Outcome analyses by age, gender, prior CDAD episode, or CDAD pre-treatment did not show significant differences for these subgroups. However, one subgroup analysis did show concerning differences. Restriction endonuclease analysis (REA) was used to identify baseline isolates of *C. difficile* in the BI group, isolates associated with increasing rates and severity of CDAD in the US in recent years. The subgroup analysis of sustained clinical response by REA type is shown in the following table.

Trial/REA Type	Fidaxomicin	Vancomycin	Difference (95% CI)
Trial 003			
BI	44/76 (58%)	52/82 (63%)	-5.5% (-20.3%, 9.5%)
Non-BI	105/126 (83%)	87/131 (66%)	16.9% (6.3%, 27.0%)
Trial 004			
BI	42/65 (65%)	31/60 (52%)	12.9% (-4.2%, 29.2%)
Non-BI	109/131 (83%)	77/121 (64%)	19.6% (8.7%, 30.0%)

From Statistical Review – Table 15, page 28

The results in the non-BI subgroup are consistent with the overall population results. However, the results in the BI subgroup showed a negative treatment difference (-5.5%) in trial 003. It should be noted that this is one of multiple subgroup analyses performed for this trial, and caution is advised when interpreting the results of such exploratory analyses. This limited evidence suggests that the advantage seen in sustained clinical response for the overall population may not apply to the BI subgroup. In essence, the superiority of fidaxomicin to vancomycin was not evident in patients infected with the BI isolate of *C. difficile*.

8. Safety

Detailed safety information was provided in the clinical review by Dr. Dmitri Iarikov. The reader is referred to this review for detailed information of the safety analyses.

The safety population for the NDA submission included 676 patients who received at least one dose of fidaxomicin and 564 fidaxomicin-treated patients in phase 3 trials. The number of patients exposed to fidaxomicin for 10 days (the proposed length of treatment) was adequate for safety analysis. The safety profile for fidaxomicin appeared to be similar to the comparator, vancomycin, in the controlled trials. Deaths were reported for 75 patients in the NDA database, one in the phase 2 dose comparison trial. In the controlled trials, the percentages of deaths in each treatment arm [36 (6.4%) for fidaxomicin and 38 (6.5%) for vancomycin) were similar. Upon review of the deaths, the medical officer thought nine deaths were possibly related to study drug (five for fidaxomicin, four for vancomycin); these deaths were attributed to possible lack of efficacy of study drug and were similar across the treatment groups.

The common treatment emergent adverse reactions reported in controlled clinical trials included nausea, vomiting and abdominal pain. Nausea was reported in 62 (11%) fidaxomicin patients and 66 (11%) vancomycin patients. Vomiting was reported in 41 (7%) and 37 (6%) patients, respectively. Abdominal pain was reported in 33 (6%) and 23 (4%) patients,

respectively. The clinical safety review described the analysis of several adverse reactions that were reported more often in the fidaxomicin group than the comparator.

Adverse reactions involving gastrointestinal (GI) hemorrhage were reported in 20 (3.5%) fidaxomicin patients and 12 (1.7%) vancomycin patients. These GI hemorrhage events were reported under several related preferred terms, including hematochezia, GI hemorrhage, and diarrhea hemorrhagic. There was one death involving GI hemorrhage, but in this instance the medical officer considered the event to be unlikely related to fidaxomicin treatment. The number of GI hemorrhage reports that were considered serious was similar for fidaxomicin and vancomycin (6 and 5, respectively). The GI hemorrhage reports did not appear to be related to baseline severity of CDAD. The reported events for vancomycin included both upper and lower GI hemorrhage events, while the events for fidaxomicin were more often lower GI hemorrhage. The reviewer could not conclude there was a causal relationship between fidaxomicin use and GI hemorrhage, noting the numerical imbalance could be a chance finding.

There were 23 (4.1%) subjects in the fidaxomicin group and 10 (1.7%) subjects in the vancomycin group with adverse events reports related to decreases in WBC counts. Reports consistent with lymphopenia were reported in 11 (1.9%) fidaxomicin patients and 5 (0.9%) vancomycin patients. Reports consistent with neutropenia were seen in 14 (2.5%) fidaxomicin patients and 6 (1%) vancomycin patients. The reason for the imbalances was not clear. Roughly half of patients with these WBC decreases in both groups had a low baseline WBC count. Twenty of the 23 patients in the fidaxomicin group had underlying comorbidities that could have contributed to the decrease in WBC count. In three patients, another reason for neutropenia was not evident; the neutropenia was considered possibly related to study drug.

Megacolon was reported as an adverse event in 3 fidaxomicin patients and no vancomycin patients. In two cases the megacolon was considered possibly related to insufficient clinical response to fidaxomicin treatment. Given the small number of cases in the controlled trials and the similar clinical response rates for fidaxomicin and vancomycin, no conclusions with regard to differences in the risk of megacolon with fidaxomicin could be made.

9. Advisory Committee Meeting

A meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) was held on April 5, 2011 to discuss the fidaxomicin NDA application. The NDA applicant presented their view of the drug development program and the clinical trial results. The FDA presentations were made by the medical officer, Dr. Dmitri Iarikov, and the statistical reviewer, Dr. Rima Izem. Dr. Iarikov provided an overview of the NDA submission and a discussion of the safety findings. The safety presentation included discussion of AE related to gastrointestinal bleeding, AE reports of neutropenia and lymphopenia, and higher systemic exposure with concomitant P-gp inhibitor use. Dr. Izem presented the results of the FDA efficacy analyses, including several sensitivity analyses evaluating different criteria for *C. difficile* recurrence. Part of Dr. Izem's presentation addressed her concerns with the interpretation of recurrence, since it is conditioned on cure. She described preference for the outcome of 'global clinical cure' because it incorporates early treatment response and remaining well through the follow-

up period. The open public hearing included four public speakers: a physician who emphasized the importance of risk factors of mechanical ventilation, age, and intensive care; and three patients who described their experiences with recurrent *C. difficile* infections.

The AIDAC deliberated on two questions. The first question asked: "Has the applicant demonstrated the safety and effectiveness of fidaxomicin for the requested indication, treatment of *Clostridium difficile*-associated diarrhea (CDAD)?" All 13 voting participants responded yes. In describing the reasons for their vote, the AIDAC members stated that the results of the pivotal trials were conclusive in demonstrating efficacy of fidaxomicin. A few members expressed some concerns about the adverse events and possible association of AE with higher systemic exposure, but these AIDAC members still considered the benefit/risk was favorable.

The second question asked: "Is the finding of lower recurrence of CDAD at Day 31 in the fidaxomicin-treated subjects of clinical significance?" Before the vote, this question engendered some requests for clarification. The AIDAC members discussed alternative questions or asked for clarifications of the question's intent. After some consideration, the AIDAC members voted 6 yes and 7 no (one no voter originally abstained). In the subsequent discussion of individual responses, the 'yes' voters agreed that information on recurrence in the early follow-up period should be included in labeling, though alternative language to recurrence was proposed. Some who voted 'yes' did object to the term 'global cure' as being unclear. The 'no' voters agreed with concerns about interpretation of recurrence, though most still supported inclusion of 'global cure' information in labeling. Taken together, the AIDAC members supported including this information in labeling, but raised concerns about misinterpretation of both terms (recurrence and global cure). The AIDAC members wanted labeling to be clear about the time period of follow-up, and the definition of terms used to describe recurrence of CDAD.

10. Pediatrics

The NDA application did not include studies of pediatric patients. All the studies submitted in the NDA application were conducted in adult patients (18 years of age or older). The applicant has proposed (b) (4)

(b) (4)

(b) (4)

(b) (4)

The recommendations at the end of this document include the postmarketing requirements for pediatric studies. It is my recommendation that the study be designed to enroll patients 6 months of age and older. I recommend a waiver of pediatric studies for children below 6 months of age. The justification for waiving studies in children <6 months of age is that the disease does not exist in this age group. A 2010 publication[1] provides information from a survey of PubMed studies about the rate of asymptomatic colonization in infants < 2 years of age. The authors state that *C. difficile* was recovered from an average of 37% of asymptomatic individuals younger than 1 month of age. Between 1 and 6 months of age, asymptomatic colonization was reported at an average rate of 30%. The rate dropped to 14% between 6 and 12 months, and 10% for children 1 years of age. This publication stated that in older children the rate of asymptomatic colonization begins "approximating the 0% to 3% carriage rate in adults".

Based on these data, there is too great a likelihood that isolation of *C. difficile* represents colonization in the 6 month age group to justify inclusion in studies of CDAD. The high rate of asymptomatic colonization in this age group suggests that infants less than 6 months of age are not susceptible to toxin produced by *C. difficile*. Even for children older than 6 months of

[1] Jangi S and Lamont JT, "Asymptomatic Colonization by Clostridium difficile in Infants: Implications for Disease in Later Life" JPGN July 2010; 51(1):2-7

age, I have some concerns that colonization in the presence of diarrhea may be confused with true CDAD disease. However, the selection criteria in the protocol will need to be sufficiently detailed to exclude diarrhea of other causes.

11. Other Relevant Regulatory Issues

The NDA application was provided as a rolling submission. The initial portion (including the CMC portion of the NDA) was submitted on September 20, 2010. The final portion of the NDA (including the clinical portion of the application) was submitted on November 29, 2010. Based on results showing superiority of fidaxomicin to vancomycin in sustained clinical response, the NDA was granted priority review status.

There were no significant financial arrangements reported with any of the clinical investigators in the application. The Division of Scientific Investigations (DSI) conducted inspections of four clinical sites and an investigation of the applicant's monitoring site. None of the findings in these inspections were considered likely to have a significant impact on data reliability. There was originally a fifth clinical site proposed for inspection, but the inspection was cancelled due to conflicting schedules and resource limitations. There were no other significant regulatory issues with the application.

12. Labeling

The proposed proprietary name, Dificid, was considered acceptable. The applicant provided labeling in the correct format with the original application, but submitted revised labeling on January 6, 2011 that was used for review. The indication proposed in the revised labeling was (b) (4) (b) (4) As noted in the discussion of the advisory committee meeting (section 9), there were concerns from the statistical reviewer about the claims for recurrence. The review team also considered CDAD to be more accurate than CDI as a description of the patient population evaluated in clinical trials. On this basis, the review team proposed an indication "for treatment of *Clostridium difficile*-associated diarrhea (CDAD). The applicant was sent a copy of the labeling changes proposed by the review team on April 29, 2011. A teleconference was held with the applicant on May 9, 2011 to discuss the proposed changes. The main issues raised by the applicant included the following:

- The applicant disagreed with the pharmacological classification as a macrolide, although they understood the concerns of the review division with the proposed classification as a (b) (4)
- The applicant wanted to include the term ' (b) (4) or ' (b) (4) in the definition of sustained clinical response.
- The applicant wanted to use (b) (4) (b) (4) (b) (4) The reviewers noted that

CDAD is more accurate in terms of what was actually evaluated (roughly 45% of patients in controlled trials had diarrhea alone), and was unlikely to be confusing to practitioners.

(b) (4)

- The applicant wanted to include the term (b) (4) spectrum in the microbiology section and a description of (b) (4)
- Since the clinical trials were designed with a follow-up visit out to 25 days after the end of treatment, the sponsor objected to reporting an analysis in labeling based on a (b) (4)

For the last point, the review team agreed that an endpoint to 25 days after then end of treatment was acceptable. The statistical reviewer provided the results of a modified sensitivity analysis (b) (4) The results of this sensitivity analysis are included in section 7 of this memo.

The labeling discussions have not been completed at the time of this writing.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the recommendations of the entire review team; I recommend approval of the NDA application for fidaxomicin.

- Risk Benefit Assessment

The two clinical trials demonstrated non-inferiority of fidaxomicin to vancomycin in the improvement of signs and symptoms of *C. difficile*-associated diarrhea (mainly documented by reduction in stool frequency) at the end of the 10 days of treatment. In addition, fidaxomicin was superior to vancomycin when assessing sustained clinical response at least three weeks after the end of treatment. This difference between treatments is related to fewer fidaxomicin-treated patients who develop diarrhea or other symptoms of CDAD that is treated with CDAD antibiotics or shown to be CDAD by laboratory testing. For assessment of risk, the safety profile of fidaxomicin and vancomycin appear similar in the controlled trials. The percentages of patients who died or experienced serious adverse events were similar between treatments. Adverse reactions that could be attributed to treatment with fidaxomicin were few, and relatively mild. The benefits of treatment of CDAD outweigh the risks associated with fidaxomicin treatment in the clinical trials reviewed.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no specific recommendations for postmarketing risk evaluation beyond routine safety monitoring.

- Recommendation for other Postmarketing Requirements and Commitments

The recommended postmarketing requirements are:

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

   Final Protocol Submission: by 9/2011
   Interim Report Submission: by 12/2012 then annually
   Study Completion Date: by 10/2016
   Final Report Submission: by 3/2017

   This study to monitor the development of fidaxomicin resistance in *C. difficile* should be considered as a post-marketing requirement.

2. Conduct a prospective clinical trial of 10 days of fidaxomicin in at least 32 pediatric patients (6 months of age and older) with *C. difficile*-associated diarrhea to evaluate the safety and pharmacokinetics (including serum and fecal concentrations) of fidaxomicin.

   Final Protocol Submission: by 10/2011
   Study Start Date: by 1/2012
   Study Completion Date: by 1/2013
   Final Report Submission: by 4/2013

   This study is the first of two studies to address the requirement for pediatric studies under PREA. The pediatric patients should be stratified by age at enrollment (recommended groups: 6-23 months, 2 years-5 years 11 months, 6 years – 11 years 11 months, and ≥ 12 years). It is recommended that the applicant consider an even larger study with randomization to at least 2 doses chosen to evaluate any exposure-response relationship.

3. Conduct a prospective, randomized clinical trial to demonstrate safety and effectiveness of fidaxomicin compared to vancomycin in pediatric patients (6 months of age and older) with *C. difficile*-associated diarrhea.

   Final Protocol Submission: by 7/2013
   Study Start Date: by 1/2014
   Study Completion Date: by 1/2017
   Final Report Submission: by 7/2017

   This study is the second of two studies to address the requirement for pediatric studies under PREA.

The following are recommended as postmarketing commitments:

4. Submit a chemistry and manufacturing controls supplement to include a test for the (b) (4) (b) (4) in the drug substance specification.
   Supplement Submission: by 11/2011

5. Conduct a prospective, randomized, comparative trial to demonstrate the efficacy of fidaxomicin in the treatment of patients with multiple recurrences of *C. difficile*-associated diarrhea.
   Final Report Submission: by 6/2016

The applicant provided their proposal for the timeline for conducting studies in e-mail correspondence dated May 18, 2011. The timelines were considered reasonable by the review division and were included in the above recommendations for postmarketing requirements and commitments.

- Recommended Comments to Applicant

The recommendations for PMR and PMC described above should be conveyed to the applicant.

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

/s/

JOHN J ALEXANDER
05/19/2011