HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DIFICID® safely and effectively.

See full prescribing information for DIFICID.

DIFICID (fidaxomicin) tablets, for oral use

Initial U.S. approval: 2011

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are proven or strongly suspected to be caused by *Clostridium difficile*.

——RECENT MAJOR CHANGES——

Contraindications (4) (03/2013)

Warnings and Precautions
Hypersensitivity reactions (5.2) (03/2013)

——INDICATIONS AND USAGE——

DIFICID is a macrolide antibacterial drug indicated in adults (≥18 years of age) for treatment of *Clostridium difficile*-associated diarrhea (1.1).

——DOSAGE AND ADMINISTRATION——

One 200 mg tablet orally twice daily for 10 days with or without food (2)

——DOSAGE FORMS AND STRENGTHS——

Film-coated tablets: 200 mg (3)

——CONTRAINDICATIONS——

Hypersensitivity to fidaxomicin. (4)

——WARNINGS AND PRECAUTIONS——

- DIFICID should not be used for systemic infections. (5.1)
- Acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash) have been reported. In the event of a severe reaction, discontinue DIFICID. (5.2)
- Development of drug-resistant bacteria: Only use DIFICID for infection proven or strongly suspected to be caused by *C. difficile*. (5.3)

——ADVERSE REACTIONS——

The most common adverse reactions are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%) (6).

To report SUSPECTED ADVERSE REACTIONS, contact Optimer Pharmaceuticals at 1-855-DIFICID (1-855-343-4243) or FDA at (1-800-FDA-1088) or *www.fda.gov/medwatch*.

——USE IN SPECIFIC POPULATIONS——

Pediatrics: The safety and effectiveness of DIFICID has not been studied in patients <18 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are proven or strongly suspected to be caused by *Clostridium difficile*.

1.1 *Clostridium difficile*-Associated Diarrhea

DIFICID is a macrolide antibacterial drug indicated in adults (≥18 years of age) for treatment of *Clostridium difficile*-associated diarrhea (CDAD).

2 DOSAGE AND ADMINISTRATION

The recommended dose is one 200 mg DIFICID tablet orally twice daily for 10 days with or without food.

3 DOSAGE FORMS AND STRENGTHS

200 mg white to off-white film-coated, oblong tablets; each tablet is debossed with “FDX” on one side and “200” on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to fidaxomicin.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Systemic Infections

Since there is minimal systemic absorption of fidaxomicin, DIFICID is not effective for treatment of systemic infections.

5.2 Hypersensitivity Reactions

Acute hypersensitivity reactions, including dyspnea, rash, pruritus, and angioedema of the mouth, throat, and face have been reported with fidaxomicin. If a severe hypersensitivity reaction occurs, DIFICID should be discontinued and appropriate therapy should be instituted.

Some patients with hypersensitivity reactions also reported a history of allergy to other macrolides. Physicians prescribing DIFICID to patients with a known macrolide allergy should be aware of the possibility of hypersensitivity reactions.

5.3 Development of Drug-Resistant Bacteria

Prescribing DIFICID in the absence of a proven or strongly suspected *C. difficile* infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of any other drug and may not reflect the rates observed in practice.

The safety of DIFICID 200 mg tablets taken twice a day for 10 days was evaluated in 564 patients with CDAD in two active-comparator controlled trials with 86.7% of patients receiving a full course of treatment.

Thirty-three patients receiving DIFICID (5.9%) withdrew from trials as a result of adverse reactions (AR). The types of AR resulting in withdrawal from the study varied considerably. Vomiting was the primary adverse reaction leading to discontinuation of dosing; this occurred at an incidence of 0.5% in both the fidaxomicin and vancomycin patients in Phase 3 studies.

Table 1. Selected Adverse Reactions with an Incidence of ≥2% Reported in DIFICID Patients in Controlled Trials

	DIFICID (N=564)	**Vancomycin (N=583)**
System Organ Class **Preferred Term**	n (%)	n (%)
Blood and Lymphatic System Disorders		
Anemia	14 (2%)	12 (2%)
Neutropenia	14 (2%)	6 (1%)
Gastrointestinal Disorders		
Nausea	62 (11%)	66 (11%)
Vomiting	41 (7%)	37 (6%)
Abdominal Pain	33 (6%)	23 (4%)
Gastrointestinal Hemorrhage	20 (4%)	12 (2%)

The following adverse reactions were reported in <2% of patients taking DIFICID tablets in controlled trials:

Gastrointestinal Disorders: abdominal distension, abdominal tenderness, dyspepsia, dysphagia, flatulence, intestinal obstruction, megacolon

Investigations: increased blood alkaline phosphatase, decreased blood bicarbonate, increased hepatic enzymes, decreased platelet count

Metabolism and Nutrition Disorders: hyperglycemia, metabolic acidosis

Skin and Subcutaneous Tissue Disorders: drug eruption, pruritus, rash

6.2 Post Marketing Experience

Adverse reactions reported in the post marketing setting arise from a population of unknown size and are voluntary in nature. As such, reliability in estimating their frequency or in establishing a causal relationship to drug exposure is not always possible.

Hypersensitivity reactions (dyspnea, angioedema, rash, and pruritus) have been reported.

7 DRUG INTERACTIONS

Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract.

7.1 Cyclosporine

Cyclosporine is an inhibitor of multiple transporters, including P-gp. When cyclosporine was co-administered with DIFICID, plasma concentrations of fidaxomicin and OP-1118 were significantly increased but remained in the ng/mL range *[see Clinical Pharmacology (12.3)]*. Concentrations of fidaxomicin and OP-1118 may also be decreased at the site of action (i.e., gastrointestinal tract) via P-gp inhibition; however, concomitant P-gp inhibitor use had no attributable effect on safety or treatment outcome of fidaxomicin-treated patients in controlled clinical trials. Based on these results, fidaxomicin may be co-administered with P-gp inhibitors and no dose adjustment is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits by the intravenous route at doses up to 12.6 and 7 mg/kg, respectively. The plasma exposures (AUC_{0-t}) at these doses were approximately 200- and 66-fold that in humans, respectively, and have revealed no evidence of harm to the fetus due to fidaxomicin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether fidaxomicin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFICID is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of DIFICID in patients <18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients in controlled trials of DIFICID, 50% were 65 years of age and over, while 31% were 75 and over. No overall differences in safety or effectiveness of fidaxomicin compared to vancomycin were observed between these subjects and younger subjects.

In controlled trials, elderly patients (≥65 years of age) had higher plasma concentrations of fidaxomicin and its main metabolite, OP-1118, versus non-elderly patients (<65 years of age) *[see Clinical Pharmacology (12.3)]*. However, greater exposures in elderly patients were not considered to be clinically significant. No dose adjustment is recommended for elderly patients.

10 OVERDOSAGE

No cases of acute overdose have been reported in humans. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day (over 100 times the human dose, scaled by weight) for 3 months.

11 DESCRIPTION

DIFICID (fidaxomicin) is a macrolide antibacterial drug for oral administration. Its CAS chemical name is Oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl]oxy]methyl]-12-[[6-deoxy-5-*C*-methyl-4-*O*-(2-methyl-1-oxopropyl)-β-D-*lyxo*-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-. The structural formula of fidaxomicin is shown in Figure 1.

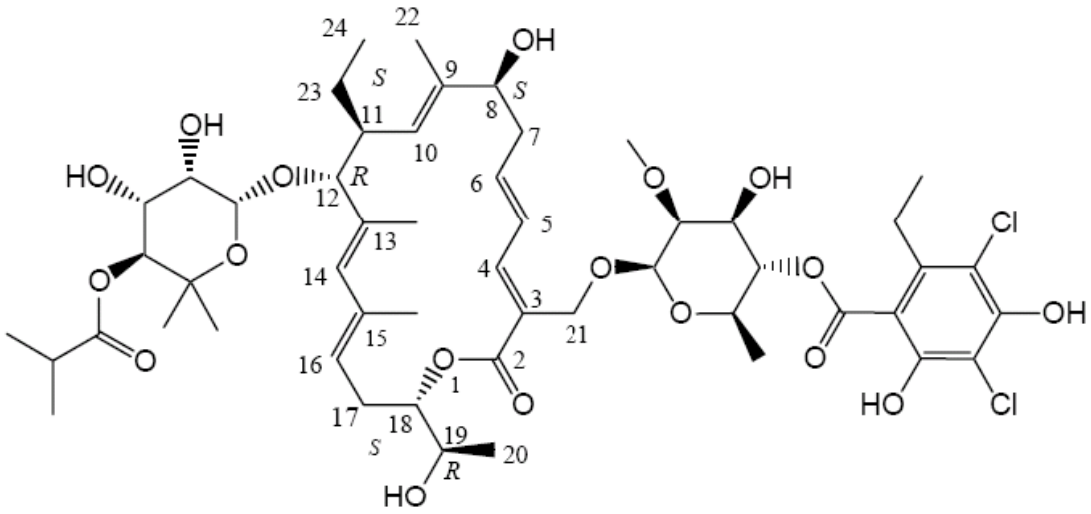

Figure 1. Structural Formula of Fidaxomicin

DIFICID tablets (200 mg) are film-coated and contain the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, hydroxypropyl cellulose, butylated hydroxytoluene, sodium starch glycolate, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, and lecithin (soy).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fidaxomicin is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Fidaxomicin acts locally in the gastrointestinal tract on *C. difficile.* In a dose-ranging trial (N=48) of fidaxomicin using 50 mg, 100 mg, and 200 mg twice daily for 10 days, a dose-response relationship was observed for efficacy.

12.3 Pharmacokinetics

The pharmacokinetic parameters of fidaxomicin and its main metabolite OP-1118 following a single dose of 200 mg in healthy adult males (N=14) are summarized in Table 2.

Table 2. Mean (± Standard Deviation) Pharmacokinetic Parameters of Fidaxomicin 200 mg in Healthy Adult Males

Parameter	Fidaxomicin		OP-1118	
	N	Value	N	Value
C_{max} (ng/mL)	14	5.20 ± 2.81	14	12.0 ± 6.06
T_{max} (h)*	14	2.00 (1.00-5.00)	14	1.02 (1.00-5.00)
AUC_{0-t} (ng-h/mL)	14	48.3 ± 18.4	14	103 ± 39.4
$AUC_{0-\infty}$ (ng-h/mL)	9	62.9 ± 19.5	10	118 ± 43.3
$t_{1/2}$ (h)	9	11.7 ± 4.80	10	11.2 ± 3.01

*T_{max}, reported as median (range)

C_{max}, maximum observed concentration; T_{max}, time to maximum observed concentration; AUC_{0-t}, area under the concentration-time curve from time 0 to the last measured concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; $t_{1/2}$, elimination half-life

Absorption

Fidaxomicin has minimal systemic absorption following oral administration, with plasma concentrations of fidaxomicin and OP-1118 in the ng/mL range at the therapeutic dose. In fidaxomicin-treated patients from controlled trials, plasma concentrations of fidaxomicin and OP-1118 obtained within the T_{max} window (1-5 hours) were approximately 2- to 6-fold higher than C_{max} values in healthy adults. Following administration of DIFICID 200 mg twice daily for 10 days, OP-1118 plasma concentrations within the T_{max} window were approximately 50%-80% higher than on Day 1, while concentrations of fidaxomicin were similar on Days 1 and 10.

In a food-effect study involving administration of DIFICID to healthy adults (N=28) with a high-fat meal versus under fasting conditions, C_{max} of fidaxomicin and OP-1118 decreased by 21.5% and 33.4%, respectively, while AUC_{0-t} remained unchanged. This decrease in C_{max} is not considered clinically significant, and thus, DIFICID may be administered with or without food.

Distribution

Fidaxomicin is mainly confined to the gastrointestinal tract following oral administration. In selected patients (N=8) treated with DIFICID 200 mg twice daily for 10 days from controlled trials, fecal concentrations of fidaxomicin and OP-1118 obtained within 24 hours of the last dose ranged from 639-2710 µg/g and 213-1210 µg/g, respectively. In contrast, plasma concentrations of fidaxomicin and OP-1118 within the T_{max} window (1-5 hours) ranged 2-179 ng/mL and 10-829 ng/mL, respectively.

Metabolism

Fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form its main and microbiologically active metabolite, OP-1118. Metabolism of fidaxomicin and formation of OP-1118 are not dependent on cytochrome P450 (CYP) enzymes.

At the therapeutic dose, OP-1118 was the predominant circulating compound in healthy adults, followed by fidaxomicin.

Excretion

Fidaxomicin is mainly excreted in feces. In one trial of healthy adults (N=11), more than 92% of the dose was recovered in the stool as fidaxomicin and OP-1118 following single doses of 200 mg and 300 mg. In another trial of healthy adults (N=6), 0.59% of the dose was recovered in urine as OP-1118 only following a single dose of 200 mg.

Specific Populations

Geriatric

In controlled trials of patients treated with DIFICID 200 mg twice daily for 10 days, mean and median values of fidaxomicin and OP-1118 plasma concentrations within the T_{max} window (1-5 hours) were approximately 2- to 4-fold higher in elderly patients (≥65 years of age) versus non-elderly patients (<65 years of age). Despite greater exposures in elderly patients, fidaxomicin and OP-1118 plasma concentrations remained in the ng/mL range *[see Use in Specific Populations (8.5)]*.

Gender

Plasma concentrations of fidaxomicin and OP-1118 within the T_{max} window (1-5 hours) did not vary by gender in patients treated with DIFICID 200 mg twice daily for 10 days from controlled trials. No dose adjustment is recommended based on gender.

Renal Impairment

In controlled trials of patients treated with DIFICID 200 mg twice daily for 10 days, plasma concentrations of fidaxomicin and OP-1118 within the T_{max} window (1-5 hours) did not vary by severity of renal impairment (based on creatinine clearance) between mild (51-79 mL/min), moderate (31-50 mL/min), and severe (≤30 mL/min) categories. No dose adjustment is recommended based on renal function.

Hepatic Impairment

The impact of hepatic impairment on the pharmacokinetics of fidaxomicin has not been evaluated. Because fidaxomicin and OP-1118 do not appear to undergo significant hepatic metabolism, elimination of fidaxomicin and OP-1118 is not expected to be significantly affected by hepatic impairment.

Drug Interactions

In vivo studies were conducted to evaluate intestinal drug-drug interactions of fidaxomicin as a P-gp substrate, P-gp inhibitor, and inhibitor of major CYP enzymes expressed in the gastrointestinal tract (CYP3A4, CYP2C9, and CYP2C19).

Table 3 summarizes the impact of a co-administered drug (P-gp inhibitor) on the pharmacokinetics of fidaxomicin *[see Drug Interactions (7.1)]*.

Table 3. Pharmacokinetic Parameters of Fidaxomicin and OP-1118 in the Presence of a Co-Administered Drug

Parameter	Cyclosporine 200 mg + Fidaxomicin 200 mg* (N=14)		Fidaxomicin 200 mg Alone (N=14)		Mean Ratio of Parameters With/Without Co-Administered Drug (90% CI) No Effect = 1.00
	N	Mean	N	Mean	
Fidaxomicin					
C_{max} (ng/mL)	14	19.4	14	4.67	4.15 (3.23-5.32)
$AUC_{0-\infty}$ (ng-h/mL)	8	114	9	59.5	1.92 (1.39-2.64)
OP-1118					
C_{max} (ng/mL)	14	100	14	10.6	9.51 (6.93-13.05)
$AUC_{0-\infty}$ (ng-h/mL)	12	438	10	106	4.11 (3.06-5.53)

* Cyclosporine was administered 1 hour before fidaxomicin
CI, confidence interval

Fidaxomicin had no significant impact on the pharmacokinetics of the following co-administered drugs: digoxin (P-gp substrate), midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). No dose adjustment is warranted when fidaxomicin is co-administered with substrates of P-gp or CYP enzymes.

12.4 Microbiology

Spectrum of Activity

Fidaxomicin is a fermentation product obtained from the Actinomycete *Dactylosporangium aurantiacum*. In vitro, fidaxomicin is active primarily against species of clostridia, including *Clostridium difficile*.

Mechanism of Action

Fidaxomicin is bactericidal against *C. difficile* in vitro, inhibiting RNA synthesis by RNA polymerases.

Mechanism of Decreased Susceptibility to Fidaxomicin

In vitro studies indicate a low frequency of spontaneous resistance to fidaxomicin in *C. difficile* (ranging from $<1.4 \times 10^{-9}$ to 12.8×10^{-9}). A specific mutation (Val-Il43-Gly) in the beta subunit of RNA polymerase is associated with reduced susceptibility to fidaxomicin. This mutation was created in the laboratory and seen during clinical trials in a *C. difficile* isolate obtained from a subject treated with DIFICID who had recurrence of CDAD. The *C. difficile* isolate from the treated subject went from a fidaxomicin baseline minimal inhibitory concentration (MIC) of 0.06 µg/mL to 16 µg/mL.

Cross-Resistance/Synergy/Post-Antibiotic Effect

Fidaxomicin demonstrates no in vitro cross-resistance with other classes of antibacterial drugs. Fidaxomicin and its main metabolite OP-1118 do not exhibit any antagonistic interaction with other classes of antibacterial drugs. In vitro synergistic interactions of fidaxomicin and OP-1118 have been observed in vitro with rifampin and rifaximin against *C. difficile* (FIC values ≤0.5). Fidaxomicin demonstrates a post-antibiotic effect vs. *C. difficile* of 6-10 hrs.

Susceptibility Testing

The clinical microbiology laboratory should provide cumulative results of the in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community acquired pathogens. These reports should aid the physician in selecting appropriate antimicrobial drug therapy.

Dilution Techniques

Quantitative anaerobic in vitro methods can be used to determine the MIC of fidaxomicin needed to inhibit the growth of the *C. difficile* isolates. The MIC provides an estimate of the susceptibility of *C. difficile* isolate to fidaxomicin. The MIC should be determined using standardized procedures.[1] Standardized methods are based on an agar dilution method or equivalent with standardized inoculum concentrations and standardized concentration of fidaxomicin powder.

Susceptibility Test Interpretive Criteria

In vitro susceptibility test interpretive criteria for fidaxomicin have not been determined. The relation of the in vitro fidaxomicin MIC to clinical efficacy of fidaxomicin against *C. difficile* isolates can be monitored using in vitro susceptibility results obtained from standardized anaerobe susceptibility testing methods.

Quality Control Parameters for Susceptibility Testing

In vitro susceptibility test quality control parameters were developed for fidaxomicin so that laboratories determining the susceptibility of *C. difficile* isolates to fidaxomicin can ascertain whether the susceptibility test is performing correctly. Standardized dilution techniques require the use of laboratory control microorganisms to monitor the technical aspects of the laboratory procedures. Standardized fidaxomicin powder should provide the MIC with the indicated quality control strain shown in Table 4.

Table 4. Acceptable Quality Control Ranges for Fidaxomicin

Microorganism	MIC Range (µg/mL)
C. difficile (ATCC 700057)	0.03-0.25

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies have not been conducted to evaluate the carcinogenic potential of fidaxomicin.

Neither fidaxomicin nor OP-1118 was mutagenic in the Ames assay. Fidaxomicin was also negative in the rat micronucleus assay. However, fidaxomicin was clastogenic in Chinese hamster ovary cells.

Fidaxomicin did not affect the fertility of male and female rats at intravenous doses of 6.3 mg/kg. The exposure (AUC_{0-t}) was approximately 100 times that in humans.

14 CLINICAL STUDIES

In two randomized, double-blinded trials, a non-inferiority design was utilized to demonstrate the efficacy of DIFICID (200 mg twice daily for 10 days) compared to vancomycin (125 mg four times daily for 10 days) in adults with *Clostridium difficile*-associated diarrhea (CDAD).

Enrolled patients were 18 years of age or older, and received no more than 24 hours of pretreatment with vancomycin or metronidazole. CDAD was defined by >3 unformed bowel movements (or >200 mL of unformed stool for subjects having rectal collection devices) in the 24 hours before randomization, and presence of either *C. difficile* toxin A or B in the stool within 48 hours of randomization. Enrolled patients had either no prior CDAD history or only one prior CDAD episode in the past three months. Subjects with life-threatening/fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon were excluded.

The demographic profile and baseline CDAD characteristics of enrolled subjects were similar in the two trials. Patients had a median age of 64 years, were mainly white (90%), female (58%), and inpatients (63%). The median number of bowel movements per day was 6, and 37% of subjects had severe CDAD (defined as 10 or more unformed bowel movements per day or WBC ≥15000/mm^3). Diarrhea alone was reported in 45% of patients and 84% of subjects had no prior CDAD episode.

The primary efficacy endpoint was the clinical response rate at the end of therapy, based upon improvement in diarrhea or other symptoms such that, in the Investigator's judgment, further CDAD treatment was not needed. An additional efficacy endpoint was sustained clinical response 25 days after the end of treatment. Sustained response was evaluated only for patients who were clinical successes at the end of treatment. Sustained response was defined as clinical response at the end of treatment, and survival without proven or suspected CDAD recurrence through 25 days beyond the end of treatment.

The results for clinical response at the end of treatment in both trials, shown in Table 5, indicate that DIFICID is non-inferior to vancomycin based on the 95% confidence interval (CI) lower limit being greater than the non-inferiority margin of -10%.

The results for sustained clinical response at the end of the follow-up period, also shown in Table 5, indicate that DIFICID is superior to vancomycin on this endpoint. Since clinical success at the end of treatment and mortality rates were similar across treatment arms (approximately 6% in each group), differences in sustained clinical response were due to lower rates of proven or suspected CDAD during the follow-up period in DIFICID patients.

Table 5. Clinical Response Rates at End-of-Therapy and Sustained Response at 25 days Post-Therapy

	Clinical Response at End of Treatment			Sustained Response at Follow-Up		
	DIFICID % (N)	Vancomycin % (N)	Difference (95% CI)	DIFICID % (N)	Vancomycin % (N)	Difference (95% CI)*
Trial 1	88% (N=289)	86% (N=307)	2.6% (-2.9%, 8.0%)	70% (N=289)	57% (N=307)	12.7% (4.4%, 20.9%)
Trial 2	88% (N=253)	87% (N=256)	1.0% (-4.8%, 6.8%)	72% (N=253)	57% (N=256)	14.6% (5.8%, 23.3%)

* Confidence interval was derived using Wilson's score method. Approximately 5%-9% of the data in each trial and treatment arm were missing sustained response information and were imputed using multiple imputation method.

Restriction Endonuclease Analysis (REA) was used to identify *C. difficile* baseline isolates in the BI group, isolates associated with increasing rates and severity of CDAD in the US in the years prior to the clinical trials. Similar rates of clinical response at the end of treatment and proven or suspected CDAD during the follow-up period were seen in fidaxomicin-treated and vancomycin-treated patients infected with a BI isolate. However, DIFICID did not demonstrate superiority in sustained clinical response when compared with vancomycin (Table 6).

Table 6. Sustained Clinical Response at 25 Days after Treatment by *C. difficile* REA Group at Baseline

Trial 1			
Initial *C. difficile* Group	**DIFICID n/N (%)**	**Vancomycin n/N (%)**	**Difference (95% CI)***
BI Isolates	44/76 (58%)	52/82 (63%)	-5.5% (-20.3%, 9.5%)
Non-BI Isolates	105/126 (83%)	87/131 (66%)	16.9% (6.3%, 27.0%)
Trial 2			
Initial *C. difficile* Group	**DIFICID n/N (%)**	**Vancomycin n/N (%)**	**Difference (95% CI)***
BI Isolates	42/65 (65%)	31/60 (52%)	12.9% (-4.2%, 29.2%)
Non-BI Isolates	109/131 (83%)	77/121 (64%)	19.6% (8.7%, 30.0%)

***** Interaction test between the effect on sustained response rate and BI versus non-BI isolates using logistic regression (p-values: trial 1: 0.009; trial 2: 0.29). Approximately 25% of the mITT population were missing data for REA group. Confidence intervals were derived using Wilson's score method.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – 7th edition. CLSI document M11-A7. CLSI, 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 2007.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DIFICID tablets are white to off-white film-coated, oblong tablets containing 200 mg of fidaxomicin; each tablet is debossed with “FDX” on one side and “200” on the other side.

DIFICID tablets are supplied as:

- Bottles of 20 tablets, (NDC 52015-080-01)
- Bottles of 60 tablets, (NDC 52015-080-02)
- 10 tablet aluminum blister cards, with 10 cards per carton, (NDC 52015-080-12)

16.2 Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

17.1 Administration with Food

Patients should be informed that DIFICID tablets may be taken with or without food.

17.2 Antibacterial Resistance

Patients should be counseled that antibacterial drugs, including DIFICID, should only be used to treat bacterial infections. They do not treat viral infections. Patients should be counseled that DIFICID only treats *Clostridium difficile*-associated diarrhea and should not be used to treat any other infection. When DIFICID tablets are prescribed, patients should be told that, although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DIFICID or other antibacterial drugs in the future.

Manufactured for Optimer Pharmaceuticals, Inc., San Diego CA 92121 by Patheon, Inc.

DIFICID® is a registered trademark of Optimer Pharmaceuticals, Inc. in the United States and other countries.

Product protected by US Patent Nos. 7,378,508; 7,507,564; 7,863,249; and 7,906,489

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