DIFICID- fidaxomicin tablet, film coated
Merck Sharp & Dohme Corp.

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

RECENT MAJOR CHANGES

Indications and Usage (1.2)	03/2019
Contraindications (4)	03/2019
Warnings and Precautions (5.1)	03/2019

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)
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*. (1.2)

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

DIFICID is contraindicated in patients who have known hypersensitivity to fidaxomicin or any other ingredient in DIFICID. (4)

WARNINGS AND PRECAUTIONS

- DIFICID should only be used for the treatment of *C. difficile*-associated diarrhea. DIFICID is not effective for treatment of other types of infections due to minimal systemic absorption of fidaxomicin. (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 (incidence ≥ 2 %) are nausea, vomiting, abdominal pain, gastrointestinal hemorrhage, anemia, and neutropenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 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 and FDA-approved patient labeling.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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).

1.2 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*. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

DIFICID is contraindicated in patients who have known hypersensitivity to fidaxomicin or any other ingredient in DIFICID *[see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Effectiveness for Infections other than *C. difficile*-Associated Diarrhea

DIFICID should only be used for the treatment of *C. difficile*-associated diarrhea. DIFICID is not effective for treatment of other types of infections due to minimal systemic absorption of fidaxomicin.

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 reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another 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

System Organ Class	DIFICID (N=564)	Vancomycin (N=583)
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

Risk Summary

The limited available data on use of DIFICID in pregnant women are insufficient to inform any drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. Embryo-fetal reproduction studies in rats and rabbits dosed intravenously during organogenesis revealed no evidence

of harm to the fetus at fidaxomicin and OP-1118 (its main metabolite) exposures 65-fold or higher than the clinical exposure at the DIFICID recommended dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In pregnant rats, fidaxomicin was administered intravenously at doses of 4, 8, and 15 mg/kg/day from gestation day 6 through 17 (during the period of organogenesis). No embryo/fetal effects were noted in this study at exposures (AUC) 193-fold higher for fidaxomicin, and 65-fold higher for OP-1118 than the clinical exposure at the DIFICID recommended dose.

In pregnant rabbits, fidaxomicin was administered intravenously at doses of 2, 4, and 7.5 mg/kg/day from gestation day 6 through 18 (during the period of organogenesis). No embryo/fetal effects were noted in this study at exposures 66-fold higher for fidaxomicin, and 245-fold higher for OP-1118 than the clinical exposure at the DIFICID recommended dose.

8.2 Lactation

Risk Summary

There is no information on the presence of fidaxomicin or its main metabolite, OP-1118, in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DIFICID and any potential adverse effects on the breastfed infant from DIFICID or from the underlying maternal condition.

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.

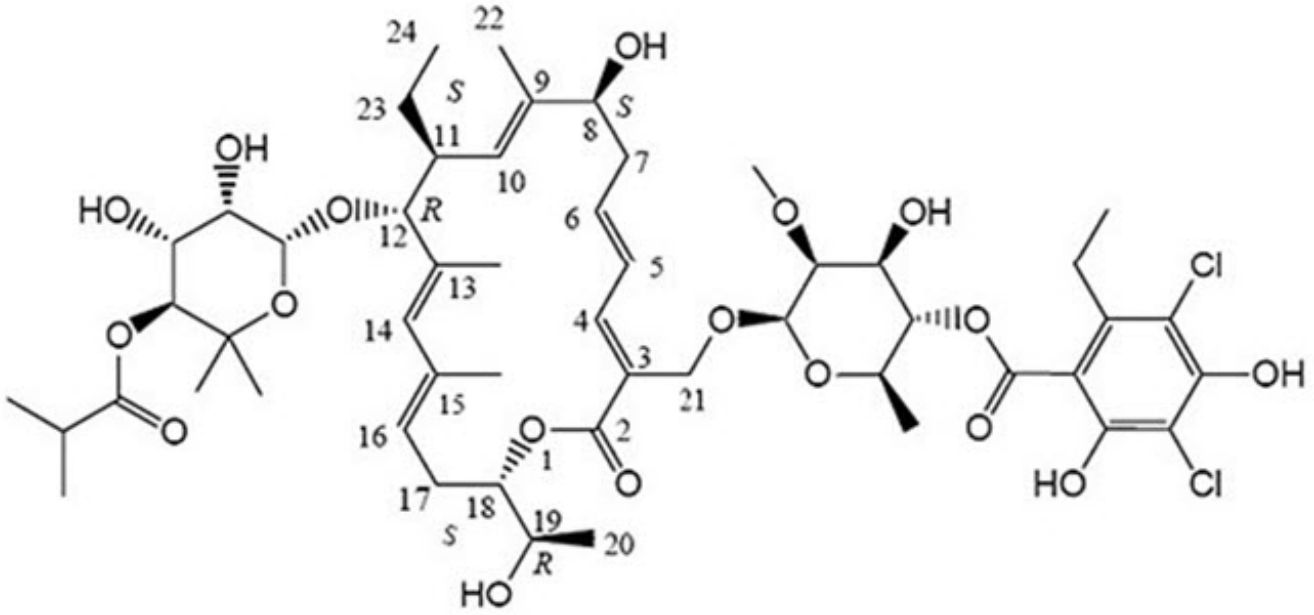

Figure 1: Structural Formula of Fidaxomicin

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

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-	9	63.9 ± 19.5	10	118 ± 43.3

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

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

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

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.

Elimination

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 Patients

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)]*.

Male and Female Patients

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.

Patients with 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.

Patients with 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 Interaction Studies

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

Mechanism of Action

Fidaxomicin is a fermentation product obtained from the Actinomycete *Dactylosporangium aurantiacum*. Fidaxomicin is bactericidal against *C. difficile in vitro*, inhibiting RNA synthesis by RNA polymerases, and demonstrates a post-antibiotic effect vs. *C. difficile* of 6-10 hrs.

Resistance

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-ll43-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.

Interaction With Other Antimicrobials

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).

Antimicrobial Activity

In vitro, fidaxomicin is active primarily against species of clostridia, including *Clostridium difficile*.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 treatment, 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 4, 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 4, 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 4: Clinical Response Rates at End-of-Treatment and Sustained Response at 25 days Post-Treatment

	Clinical Response at End of Treatment			**Sustained Response at 25 days Post-Treatment**		
	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 (CI) 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 5).

Table 5: 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 (CI) were derived using Wilson's score method.

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).

16.2 Storage

Storage: 20°-25°C (68°-77°F); excursions permitted to 15° - 30°C (59° - 86°F). See USP controlled room temperature.

Store in the original bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Administration with Food

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

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 (e.g., the common cold). When DIFICID is prescribed to treat a *C. difficile* infection, 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: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: Patheon Inc.
Mississauga, Ontario, L5N 7K9, Canada

For patent information: www.merck.com/product/patent/home.html

uspi-mk5119-t-1904r002

Patient Information
DIFICID® (dih-fih-sid)

(fidaxomicin)
tablets, for oral use

What You Need to Know About Your Medicine

- Before you take DIFICID, be sure you understand what it is for and how to take it.
- If you have questions about DIFICID, ask your doctor or pharmacist.
- Remember that your doctor has prescribed DIFICID only for you. Never give this medicine to anyone else.
- Keep this Patient Information for DIFICID so you can read it again.

What is DIFICID?

DIFICID is an antibiotic medicine used to treat an infection called *Clostridium difficile*-associated diarrhea (CDAD) in adults 18 years of age and older. *Clostridium difficile* (C-diff) is a bacterium that can cause an infection that can damage your colon and cause stomach pain and severe diarrhea.

- DIFICID is not to be used to treat other types of infections in the body.
- Sometimes infections are caused by viruses rather than bacteria. Antibiotic medicines including DIFICID do not kill viruses.

It is not known if DIFICID is safe and effective in children under 18 years old.

Who should not take DIFICID?

Do not take DIFICID if you are allergic to fidaxomicin, or any other ingredient in DIFICID. See the end of this Patient Information for a complete list of ingredients in DIFICID.

What should I tell my doctor before taking DIFICID?

Pregnancy

- If you are pregnant or plan to become pregnant, tell your doctor before you take DIFICID.
- It is not known if DIFICID will harm your baby while you are pregnant.
- If you are pregnant, you and your doctor should decide together if you will take DIFICID.

Breastfeeding

- If you are breastfeeding or plan to breastfeed, tell your doctor before you take DIFICID.
- It is not known if DIFICID passes into breast milk.
- If you are breastfeeding, you and your doctor should decide together if you will take DIFICID.

Other Medicines

- **Tell your doctor about all of the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal and dietary supplements.
- Know the medicines you take. Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine.

Allergic Reactions

- See "**Who should not take DIFICID?**"
- If you are allergic to other kinds of antibiotics called macrolides (for example: azithromycin (Zithromax) or clarithromycin (Biaxin)) or any other ingredient in DIFICID, tell your doctor. See the end of this Patient Information for a complete list of ingredients in DIFICID.

How do I take DIFICID?

- Take DIFICID exactly as prescribed by your doctor.
- Take 1 tablet twice a day (approximately every 12 hours). For example, if you take your first tablet at 8:00 a.m. you should take your second tablet at 8:00 p.m.
- You can take DIFICID with or without food.
- **Do not** skip any doses or stop taking DIFICID until you finish your prescribed treatment, even if you begin to feel better, unless you have a serious allergic reaction (see "**What are the possible side effects of DIFICID?**").
  This will lower the chance that the bacteria will become resistant to DIFICID. If this happens, DIFICID and other antibiotic medicines may not work in the future.

What are the possible side effects of DIFICID?

DIFICID can cause serious side effects, including:

- **Allergic reaction**. If you get a severe allergic reaction while taking DIFICID, including problems breathing or shortness of breath, rash, itching or hives, or swelling of the mouth, throat, or face, stop taking DIFICID and get emergency medical help right away.

Common side effects of DIFICID include:

The most common side effects of DIFICID include:

- nausea
- vomiting
- stomach pain
- bleeding in the stomach or intestines
- low red blood cell count (anemia)
- low white blood cell count (neutropenia)

Other less common side effects of DIFICID may include:

- Changes in your skin
  - swelling of any body part (such as your face, lips, tongue or around your eyes)
  - itching
  - rash or skin reaction
- Changes in your stomach or intestines
  - bloating
  - stomach tenderness
  - heartburn
  - problems swallowing
  - passing gas
  - intestinal blockage
  - serious bowel inflammation (toxic megacolon)
- Changes in your blood work
  - high levels of an enzyme called alkaline phosphatase in your blood
  - low levels of blood bicarbonate
  - high levels of acid in your blood (metabolic acidosis)
  - low platelet count (important for clotting and to control bleeding)
  - high blood sugar (hyperglycemia)
  - abnormal liver function tests

If you have any side effect that bothers you or does not go away, tell your doctor.

There may be other side effects to DIFICID that are not listed. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DIFICID?

- Store DIFICID at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep DIFICID in its original bottle until you are ready to take it.

Keep DIFICID and all medicines out of the reach of children.

General information about the safe and effective use of DIFICID.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information. Do not take DIFICID for a condition for which it was not prescribed. Do not give DIFICID to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about DIFICID that is written for health professionals.

What if I have questions?

- Call your doctor.
- Call Merck, the company that makes DIFICID, at 1-800-444-2080.
- Go to the website – www.DIFICID.com.
- You can also find the full prescribing information written for doctors at www.DIFICID.com

What are the ingredients in DIFICID?

- **Active ingredient**: fidaxomicin.
- **Inactive ingredients**: butylated hydroxytoluene, hydroxypropyl cellulose, lecithin (soy), magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinized starch, sodium starch glycolate, talc, and titanium dioxide.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: Patheon Inc., Missassauga, Ontario, L5N 7K9 Canada

For patent information: www.merck.com/product/patent/home.html. The trademarks depicted herein are owned by their respective companies.

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This Patient Information has been approved by the U.S. Food and Drug Administration
Issued: 04/2019

PRINCIPAL DISPLAY PANEL - 200 mg Tablet Bottle Carton

NDC 52015-080-01
20 tablets

DIFICID®
(fidaxomicin) tablets

200 mg per tablet

Rx only

DIFICID

fidaxomicin tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:52015-080
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FIDAXOMICIN (UNII: Z5N076G8YQ) (FIDAXOMICIN - UNII:Z5N076G8YQ)	FIDAXOMICIN	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	

Product Characteristics			
Color	white (white to off-white)	**Score**	no score
Shape	CAPSULE (oblong)	**Size**	14mm
Flavor		**Imprint Code**	FDX;200
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:52015-080-01	1 in 1 CARTON	05/27/2011	
1		20 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA201699	05/27/2011	

Labeler - Merck Sharp & Dohme Corp. (001317601)

Revised: 4/2019 Merck Sharp & Dohme Corp.