PRODUCT MONOGRAPH

Pr DIFICID®

fidaxomicin

Film-coated tablet, 200 mg

Antibacterial agent

Merck Canada Inc.
16750 route Transcanadienne
Kirkland, QC H9H 4M7
www.merck.ca

Date of Preparation:
January 29, 2018

Submission Control No: 209686

Table of Contents

Pr DIFICID®

fidaxomicin

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film-coated tablet/200 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DIFICID® (fidaxomicin) is indicated in adults (≥18 years of age) for the treatment of *Clostridium difficile* infection (CDI).

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*.

Geriatrics (≥65 years of age):
Greater systemic drug exposures were seen in elderly patients compared to those <65 years of age, but the magnitudes of increase were not considered to be clinically significant (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**). No dose adjustment is recommended for elderly patients.

Pediatrics (<18 years of age):
The safety and efficacy of DIFICID® in patients below18 years of age have not been established. No data are available.

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 susceptible bacteria. 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.

CONTRAINDICATIONS

Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Not for Systemic Infections

Since there is minimal systemic absorption of fidaxomicin, DIFICID® should not be used for the treatment of systemic infections.

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.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies have not been conducted to evaluate the carcinogenic potential of fidaxomicin. Under the conditions tested, fidaxomicin was not mutagenic in the Ames assay and did not show a biologically significant increase in DNA damage in the rat micronucleus and comet assays. However, fidaxomicin was clastogenic in Chinese hamster ovary cells (see **TOXICOLOGY**).

Cardiovascular

Electrocardiogram (ECG) parameters and QT intervals (QTc) were measured in patients participating in Phase 3 studies. No clinically significant changes from baseline to end of therapy in mean ECG parameters were seen. There was no evidence of QTc prolongation with DIFICID® treatment and there was no association between QTc prolongation and plasma levels of fidaxomicin or OP-1118, its main metabolite.

In an in vitro electrophysiology study, fidaxomicin and its main metabolite, OP-1118, had no effect on the hERG channel.

Gastrointestinal

Due to limited clinical data, DIFICID® should be used with caution in patients with pseudomembranous colitis, fulminant or life threatening CDI.

There are no data in patients with concomitant inflammatory bowel disease. DIFICID® should be used with caution in these patients due to the risk of enhanced absorption and potential risk of systemic adverse events.

Patients with more than one previous episode of CDI within the 3 months prior to initiation of treatment have not been studied.

Hepatic/Biliary/Pancreatic
There are limited clinical data in patients with severe hepatic insufficiency. Patients with severe hepatic impairment may have increased exposure to DIFICID®. For these reasons, DIFICID® should be used with caution in such patients.

Hypersensitivity
Acute hypersensitivity reactions, such as 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 macrolides. Physicians prescribing DIFICID® to patients with a known macrolide allergy should be aware of the possibility of hypersensitivity reactions.

Renal
There are limited clinical data in patients with severe renal insufficiency. Therefore, DIFICID® should be used with caution in such patients.

Special Populations

Pregnant Women: There are no data available on the use of DIFICID® in pregnant women. 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 the human exposure at the therapeutic dose level, respectively, and have revealed no evidence of harm to the fetus due to fidaxomicin.

Because animal reproduction studies are not always predictive of human response, DIFICID® should not be used during pregnancy unless the expected benefits to the mother outweigh the potential risks to the fetus.

Nursing Women: It is not known whether fidaxomicin is excreted in human milk. Because many drugs are excreted in human milk, DIFICID® should not be administered to a nursing woman unless the expected benefit to the mother outweighs the potential risk to the infant.

Pediatrics (<18 years of age): The safety and effectiveness of DIFICID® in patients <18 years of age have not been established.

Geriatrics (≥65 years of age): Of the total number of patients with CDI enrolled in controlled trials of DIFICID®, almost half (272, 48.2%) of the DIFICID®-treated patients were 65 years of age and over. 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 **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Geriatrics**). However, the magnitudes of increase in exposures in elderly patients were not considered to be clinically significant.

No dose adjustment is recommended for elderly patients.

Susceptibility/Resistance

Development of Drug Resistant Bacteria: Prescribing DIFICID® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall rate of adverse drug reactions assigned by the clinical investigators as being possibly or definitely related to DIFICID® in Phase 3 clinical trials was 10.6%. The most common adverse drug reactions in patients receiving DIFICID® were nausea (2.7%), constipation (1.2%), and vomiting (1.2%). The majority of adverse drug reactions were reported as mild or moderate in severity. No serious adverse drug reaction considered to be related to DIFICID® by the investigator was reported by more than 1 subject.

The overall incidence of adverse events leading to study withdrawal was similar for the DIFICID® (n=33, 5.9%) and comparator (n=40, 6.9%) groups. The types of adverse events resulting in withdrawal from the study were varied. Vomiting was the primary adverse event leading to drug discontinuation for patients receiving DIFICID®, and occurred at a rate of 0.5%.

Some patients (2.8%) receiving DIFICID® during the Phase 3 trials experienced rash, pruritus, or rash-like symptoms. Reported symptoms were mild and self-limiting or resolved with anti-histamine treatment.

Compared to the comparator, more patients treated with DIFICID® experienced neutropenia (2% versus 1%) and gastrointestinal hemorrhage (4% versus 2%). However, these events were considered not drug-related by the investigators.

The overall incidence of mild, moderate, and severe adverse events was similar for the DIFICID® and comparator groups.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety of DIFICID® 200 mg tablets taken twice a day for 10 days was evaluated in 564 patients with *C. difficile* infection in two active-comparator, double-blind, controlled trials with 86.7% of patients receiving a full course of treatment.

Adverse drug reactions (as judged by the investigator to be possibly or definitely related to DIFICID®) that occurred at a rate of ≥1% are shown in Table 1 and the Less Common Clinical Trial Adverse Drug Reactions are presented below the table.

Table 1 - Adverse Drug Reactions Occurring in ≥1% Patients in the DIFICID® Group (Pooled Phase 3 Studies: Safety Population)

System Organ Class Preferred Term	DIFICID® (N=564) n (%)	Vancomycin (N=583) n (%)
Any Adverse Drug Reaction	60 (10.6)	65 (11.1)
Gastrointestinal disorders	33 (5.9)	33 (5.7)
Nausea	15 (2.7)	20 (3.4)
Vomiting	7 (1.2)	8 (1.4)
Constipation	7 (1.2)	3 (0.5)

Less Common Clinical Trial Adverse Drug Reactions (<1% and reported by at least two subjects)

Gastrointestinal Disorders: abdominal distension, flatulence, dry mouth
Hepatobiliary Disorders: alanine aminotransferase increased
Metabolism and Nutrition Disorders: anorexia
Nervous System Disorders: dizziness, dysgeusia, headache

Post-Market Adverse Drug Reactions

Adverse reactions reported in the post marketing 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.

Acute hypersensitivity reactions have been reported during post marketing such as rash, pruritus, angioedema and dyspnea.

DRUG INTERACTIONS

Overview

Metabolism of fidaxomicin is not primarily dependent on human cytochrome P450 (CYP) enzymes and fidaxomicin does not induce or inhibit these enzymes in vitro.

In vitro, fidaxomicin and its main metabolite, OP-1118, are substrates and inhibitors of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract. In vivo data suggest that fidaxomicin may be a mild to moderate inhibitor of intestinal P-gp.

Drug-Drug Interactions

In vivo in healthy volunteers, fidaxomicin did not have a clinically relevant effect on the CYP2C9 substrate warfarin, CYP3A4/5 substrate midazolam, and CYP2C19 substrate

omeprazole. Based on these results, no dose adjustment is warranted when DIFICID® is co-administered with CYP substrate compounds.

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

When digoxin, a P-gp substrate, was co-administered with DIFICID® (200 mg twice daily) in healthy volunteers, digoxin C_{max} and AUC increased by 14% and 12%, respectively. This effect of fidaxomicin on digoxin exposure is not considered clinically relevant. However, a larger effect on P-gp substrates with lower bioavailability and that are more sensitive to intestinal P-gp inhibition cannot be excluded.

Table 2 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
P-glycoprotein inhibitors			
Cyclosporine	CT	↑ fidaxomicin C_{max}, AUC	Co-administration of single doses of the P-gp inhibitor cyclosporine A and DIFICID® in healthy volunteers resulted in a 4- and 2-fold increase in fidaxomicin C_{max} and AUC, respectively and a 9.5- and 4-fold increase in C_{max} and AUC of the main active metabolite OP-1118. Plasma concentrations of fidoxamicin and OP-1118 remained in the ng/mL range. No dose adjustment is recommended. The effect of fidaxomicin on cyclosporine pharmacokinetics has not been investigated.
P-glycoprotein substrates			
Digoxin	CT	↑ digoxin C_{max}, AUC	Digoxin co-administered with DIFICID® (200 mg twice daily) in healthy volunteers resulted in an increase in digoxin C_{max} by 14% and AUC by 12%. This effect of fidaxomicin on digoxin exposure is not considered clinically relevant. No dose adjustment is recommended.
CYP2C9 substrate			
Warfarin	CT	No change	A drug-drug interaction study was carried out using CYP2C9 substrate warfarin. The results of this study indicated that co-administration with DIFICID® (q12h) did not result in a statistically significant change in the pharmacokinetics of warfarin. No dose adjustment is recommended.

Proper name	Ref	Effect	Clinical comment
CYP3A4 substrate			
Midazolam	CT	No change	A drug-drug interaction study was carried out using CYP3A4/5 substrate midazolam. The results of this study indicated that co-administration with DIFICID® (q12h) did not result in a statistically significant change in the pharmacokinetics of midazolam. No dose adjustment is recommended.
CYP2C19 substrate			
Omeprazole	CT	No change	A drug-drug interaction study was carried out using CYP2C19 substrate omeprazole. The results of this study indicated that co-administration with DIFICID® (q12h) did not result in a statistically significant change in the pharmacokinetics of omeprazole. No dose adjustment is recommended.

CT = Clinical Trial

Drug-Food Interactions

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% in the fed versus fasted state, respectively, while AUC_{0-t} remained unchanged. As the systemic exposure to fidaxomicin and its main metabolite were equivalent in the fed state as compared to the fasted state, DIFICID® may be administered with or without food.

Drug-Herb Interactions

Drug-Herb interactions have not been studied.

Drug-Laboratory Interactions

Drug-Laboratory test interactions have not been studied.

Drug-Lifestyle Interactions

Drug-Lifestyle interactions have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

DIFICID® (fidaxomicin) tablets can be administered with or without food (see **DRUG INTERACTIONS, Drug-Food Interactions**).

No dose adjustment in adults is necessary based on age or gender. No dose adjustment is recommended based on renal function or hepatic impairment (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and Renal)**.

Recommended Dose and Dosage Adjustment

The recommended dose for adults ≥18 years of age is one 200-mg DIFICID® tablet orally twice daily for 10 days with or without food.

Missed Dose
If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, no additional dose should be taken and the regular dosing schedule should be resumed.

No more than two doses of DIFICID® (1 tablet twice a day) should be taken in a 24-hour period.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No cases of acute overdose have been reported in humans.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Fidaxomicin is a narrow spectrum macrocyclic antibacterial. Fidaxomicin is bactericidal against *C. difficile* in vitro, with a post-antibiotic effect of 6-10 hours. It acts via inhibition of RNA synthesis by RNA polymerases. It interferes with RNA polymerase at a site distinct from that of rifamycins. Inhibition of the Clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E. coli* enzyme (1 μM vs. 20 μM), partly explaining the significant specificity of fidaxomicin activity. Fidaxomicin has also been shown to inhibit *C. difficile* sporulation and toxin production in vitro (see **MICROBIOLOGY**).

Pharmacodynamics
Fidaxomicin acts locally on *C. difficile* in the gastrointestinal tract with minimal systemic absorption and fecal concentrations in the colon that exceed the MIC_{90} of *C. difficile* throughout the dosing interval. As a topical agent, systemic pharmacokinetic/pharmacodynamic relationships cannot be established, however in vitro data show fidaxomicin to have time-dependent bactericidal activity and suggest time over minimal inhibitory concentration (MIC) may be the parameter most predictive of clinical efficacy.

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 3 below.

Table 3 - Mean (± Standard Deviation) Pharmacokinetic Parameters of Fidaxomicin 200 mg and OP-1118 in Healthy Adult Males

	C_{max} (ng/mL)	T_{max} (hr)*	$t_{½}$ (hr)	AUC_{0-t} (ng-hr/mL)	$AUC_{0-\infty}$ (ng-hr/mL)
Fidaxomicin	5.20 ± 2.81 (n=14)	2.00 (1.00-5.00) (n=14)	11.7 ± 4.80 (n=9)	48.3 ± 18.4 (n=14)	62.9 ± 19.5 (n=9)
OP-1118	12.0 ± 6.06 (n=14)	1.02 (1.00-5.00) (n=14)	11.2 ± 3.01 (n=10)	103 ± 39.4 (n=14)	118 ± 43.3 (n=10)

* T_{max} reported as median (range).
C_{max}, maximum observed concentration.
T_{max}, time to maximum observed concentration.
$t_{1/2}$, elimination half-life.
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.

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 DIFICID®-treated patients with CDI in controlled trials, plasma concentrations of fidaxomicin and its main metabolite 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 Day 1 and Day 10.

Following high fat meal administration, mean C_{max} for fidaxomicin and OP-1118 in plasma were 21% and 33% lower following the high fat meal vs. fasting, but the extent of exposure (AUC_{0-t}) was equivalent.

Distribution: Fidaxomicin is mainly confined to the gastrointestinal tract following oral administration. In patients 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 5.0-7630.0 µg/g and 63.4-4170.0 µg/g, respectively. In contrast, plasma concentrations of fidaxomicin and OP-1118 at 3-5 hours post-dose (Day 10) ranged between 0.3-191.0 ng/mL and 1.1-871.0 ng/mL, respectively. The volume of distribution in humans is unknown, due to very limited absorption of fidaxomicin. Plasma protein binding of fidaxomicin in humans is 97%.

Metabolism: No extensive analysis of metabolites in plasma has been performed due to low levels of systemic absorption of fidaxomicin. Fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form its main and microbiologically active metabolite, OP-1118.
In vitro metabolism studies indicate that the formation of OP-1118 is not dependent on CYP450 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. The main elimination pathways of systemically available fidaxomicin have not been characterized in humans. Elimination through urine is negligible (<1%). Only very low levels of OP-1118 and no fidaxomicin were detectable in human urine following single dose of 200 mg. The half life of fidaxomicin is approximately 8-10 hours.

Special Populations and Conditions

Geriatrics: 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 2-4 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. This difference is not considered to be clinically relevant.

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 these parameters.

Hepatic Insufficiency: 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. Limited data from patients with an active history of chronic hepatic cirrhosis in the Phase 3 studies showed that median plasma levels of fidaxomicin and OP-1118 may be approximately 2 and 3 fold higher, respectively, than in non-cirrhotic patients, but plasma levels remained in the low ng/mL range. No dose adjustment is recommended based on hepatic function.

Renal Insufficiency: 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.

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DIFICID® tablets are white to off-white film-coated, oblong tablets; each tablet is debossed with "FDX" on one side and "200" on the other side.

DIFICID® tablets (200 mg) are film-coated and contain the following inactive ingredients:

Tablets:
Microcrystalline Cellulose
Pregelatinised Starch
Hydroxypropyl Cellulose
Butylated Hydroxytoluene
Magnesium Stearate
Sodium Starch Glycolate

Coat:
Polyvinyl Alcohol
Titanium Dioxide
Talc
Polyethylene glycol
Lecithin (Soy)

DIFICID® tablets are supplied as:

- 30 cc HDPE bottles capped with induction seal closure; 20 film-coated tablets per bottle
- 60 cc HDPE bottles capped with induction seal closure; 60 film-coated tablets per bottle
- 20 × 1 alu/alu perforated unit dose blisters (10 film-coated tablets per card; 2 cards per carton)
- 100 × 1 alu/alu perforated unit dose blisters (10 film-coated tablets per card; 10 cards per carton)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

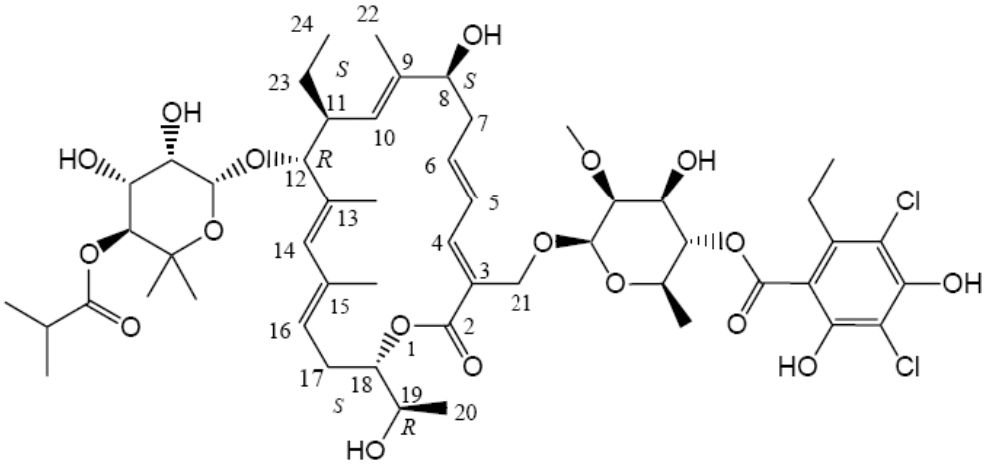
Drug Substance

Proper name: fidaxomicin

Chemical name: 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-[(1R)-1-hydroxyethyl]-9,13,15-trimethyl-, (3E,5E,8S,9E,11S,12R,13E,15E,18S)-.

Molecular formula and molecular mass: $C_{52}H_{74}Cl_2O_{18}$; 1058.04

Structural formula:



Physicochemical properties: White to off-white powder

Solubility: Freely soluble in tetrahydrofuran, dimethyl sulfoxide and methanol. Soluble in acetone and sparingly soluble in ethyl acetate, ethanol (200 proof), dichloromethane and acetonitrile. Slightly soluble in isopropanol and practically insoluble in water.

pKa: 9.31 at room temperature

Partition coefficient: Log P is 3.7 (n-octanol-water system)

CLINICAL TRIALS

DIFICID® was studied for the treatment of *C. difficile* infection in 2 pivotal clinical studies.

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in the treatment of *C. difficile* infection

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender M/F
101.1.C.003 Phase 3 (1)	Multi-National, Multi-Center, Double-Blind, Non-inferiority, Randomized, Parallel Group Study	DIFICID® (400 mg; 200 mg q12h) vs. Vancomycin (500 mg;125 mg q6h) 10 days	DIFICID®: 300; Vancomycin: 323	61.6 ±16.9 (18-94)	DIFICID®: 132/168; Vancomycin: 146/177
101.1.C.004 Phase 3 (2)	Multi-National, Multi-Center, Double-Blind, Non-inferiority, Randomized, Parallel Group Study	DIFICID® (400 mg; 200 mg q12h) vs. Vancomycin (500 mg;125 mg q6h) 10 days	DIFICID®: 264; Vancomycin: 260	63.4 ±18.1 (18-94)	DIFICID®: 110/154; Vancomycin: 96/164

Enrolled patients were 18 years of age or older and received no more than 24 hours of pretreatment with vancomycin or metronidazole. CDI 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 CDI history or only one prior CDI episode in the past three months. Subjects with life-threatening/fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon were excluded. Patients with fulminant colitis and patients with multiple episodes (defined as more than one prior episode within the previous 3 months) of CDI were also excluded in the studies.

The demographic profile and baseline CDI characteristics of enrolled subjects were similar in the two Phase 3 trials. Patients had a median age of 64 years, were mainly white (90%), female (58%), and inpatients (63%). Almost half of the patients (49.4%) were aged ≥65 years. Concomitant antibiotics were received by 27.5% (275/999) at some time during the studies, and 19.2% (192/999) of patients received antibiotics concurrently with study drug.

At enrollment, the median number of bowel movements per day was 6 and 25.3% of subjects had severe CDI (defined as a diagnosis of CDI with at least one of the following: fever [>38.5°C], or marked leukocytosis [leukocyte count >15 × 10^9/L], or rise in serum creatinine [≥1.5 mg/dL])

Approximately 84% of subjects had no prior CDI episode within the previous 3 months.

Study results

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 CDI treatment was not needed. Additional secondary efficacy endpoints were recurrence and sustained clinical response. Sustained clinical response was evaluated only for patients who were clinical successes at the end of therapy. Sustained clinical response was defined as achieving clinical response at the end of therapy and not having a recurrence of CDI at any time up through 28 days beyond the end of therapy.

The results for clinical response in the modified intent-to-treat (mITT) population at the end of therapy 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%.

Table 5 - Clinical response rates at end-of-therapy and sustained clinical response at 28 days post-therapy (mITT) in Phase 3 Studies

	Clinical Response at End of Therapy			Sustained Clinical Response at 28 Days Follow-Up		
Study	**DIFICID® n/N (%)**	**Vancomycin n/N (%)**	**Difference (95% CI)***	**DIFICID® n/N (%)**	**Vancomycin n/N (%)**	**Difference (95% CI)***
101.1.C.003	255/289 (88.2)	263/307 (85.7)	2.6 (-2.9, 8.0)	215/289 (74.4)	197/307 (64.2)	10.2 (2.8,17.5) p=0.007
101.1.C.004	222/253 (87.7)	222/256 (86.7)	1.0 (-4.8, 6.8)	194/253 (76.7)	162/256 (63.3)	13.4 (5.4, 21.1) p=0.001

* Confidence interval was using a 2-sided method recommended by Agresti and Caffo (2000) and p-value using Pearson's chi-square test.

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 therapy and mortality rates (approximately 6% in each group) were similar across treatment arms, differences in sustained clinical response were due to lower rates of proven or suspected CDI recurrence during the follow-up period in DIFICID® patients. Proven or suspected CDI recurrence rates through 28 days post-therapy for those subjects who were clinical successes at the end of therapy are shown in Table 6.

Table 6 - Proven or suspected CDI recurrence rates in Phase 3 studies (mITT population)

Study	DIFICID® n/N (%)	Vancomycin n/N (%)	Difference (95% CI)*
101.1.C.003	40/255 (15.7)	66/263 (25.1)	-9.4 (-16.2,-2.5) p=0.008
101.1.C.004	28/222 (12.6)	60/222 (27.0)	-14.4 (-21.6,-7.0) p<0.001

* Confidence interval was using a 2-sided method recommended by Agresti and Caffo (2000) and p-value using Pearson's chi-square test.

Restriction endonuclease analysis (REA) was used to identify *C. difficile* baseline isolates in the BI group, isolates associated with increasing rates and severity of CDI in Canada in the years prior to the clinical trials. Similar rates of clinical response at the end of therapy and similar rates of recurrence of CDI during the follow-up period were seen in DIFICID®-treated and vancomycin-treated patients infected with a BI isolate. DIFICID® did not demonstrate superiority in sustained clinical response against the BI isolate when compared with vancomycin (Table 7).

Table 7 - Sustained clinical response at 28 days after therapy by *C. difficile* REA group at baseline in Phase 3 studies (mITT population)

Initial *C. Difficile* Group	DIFICID® n/N (%)	Vancomycin n/N (%)	Difference (95% CI)*
Study 101.1.C.003			
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)
Study 101.1.C.004			
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.

Results for all endpoints were consistent with the primary findings across other subgroups analyzed (including age, sex, race, disease severity, use of concomitant antibiotics, and in-patient vs. out-patient status).

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

The hamster model is a well-studied, reproducible model of fatal *C. difficile* disease. Fidaxomicin is able to rescue animals infected with an otherwise lethal inoculum of toxigenic *C. difficile*. Using this model, the ED_{50} of fidaxomicin was ≤0.3 mg/kg when hamsters were infected with spores of toxigenic *C. difficile* ATCC 43255. A 7-day treatment course of fidaxomicin at 0.8 or 2.5 mg/kg was as effective as vancomycin (5 mg/kg) or metronidazole (100 mg/kg) in rescuing animals from otherwise fatal CDI.

Safety Pharmacology
Studies were conducted to assess the impact of fidaxomicin on the cardiovascular, respiratory, and central nervous systems. Neither fidaxomicin nor its metabolite OP-1118 inhibited the hERG-related potassium current in vitro, and in a cardiovascular safety study in dogs, the no-observable adverse effect level was the highest dose studied, which produced a systemic exposure 351-fold over human exposure at the therapeutic dose level. Intravenous dosing of fidaxomicin to rats produced a systemic exposure 84-fold over human exposure and had no impact on respiratory parameters or CNS pharmacological response, as assessed by a functional observational battery.

Pharmacokinetics
Fidaxomicin is largely confined to the gut after oral administration. Oral bioavailability is less than 3% in dogs, and the drug is largely excreted in the feces. In a radiolabelled mass balance study of oral fidaxomicin in dogs, over 99% of the recovered radioactivity was found in the feces. Following intravenous dosing in rats, rabbits, and dogs, the volume of distribution was generally less than total body water, indicating that fidaxomicin does not strongly partition out of total body water. As in humans, the plasma protein binding of fidaxomicin in rats, rabbits, and dogs exceeds 96%. The primary metabolic transformations (hydrolysis, accompanied by minor amounts of acyl migration) occur at the isobutyryl ester, along with a small amount of glucuronidation and sulfation. A study of biliary excretion in dogs showed that fidaxomicin, its primary metabolite OP-1118, and their sulfated and glucuronidated forms are secreted into the bile. Biliary excretion of fidaxomicin and OP-1118 accounted for less than 1% of the administered dose.

Human Pharmacology
The pharmacodynamics and pharmacokinetic of fidaxomicin were described previously in **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**, **Pharmacokinetics**.

MICROBIOLOGY

Mechanism of Action
Fidaxomicin is a macrocyclic antibacterial. Fidaxomicin is bactericidal and inhibits RNA synthesis by bacterial RNA polymerase. It interferes with RNA polymerase at a distinct site from that of rifamycins. Inhibition of the Clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E. coli* enzyme (1 μM vs. 20 μM), partly explaining the significant specificity of fidaxomicin activity. Fidaxomicin has been shown to inhibit *C. difficile* sporulation and toxin production in vitro.

Spectrum of Activity
Fidaxomicin is a narrow spectrum antimicrobial drug with bactericidal activity against *C. difficile.* Fidaxomicin has an MIC_{90} of 0.25 mg/L against *C. difficile.* Its main metabolite, OP-1118, has an MIC_{90} of 8 mg/L. Gram negative organisms are intrinsically not susceptible to fidaxomicin.

Effect on Intestinal Flora

Studies have demonstrated that fidaxomicin treatment did not affect *Bacteroides* concentrations or other major components of the microbiota in the feces of CDI patients.

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-ll43-Gly) in the beta subunit of RNA polymerase is associated with reduced susceptibility to fidaxomicin. This mutation was found after sequencing a *C. difficile* isolate in the laboratory that was obtained from a patient treated with DIFICID® who had recurrence of CDI. The *C. difficile* isolate from the treated patient 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, including macrolides. Fidaxomicin and its main metabolite OP-1118 do not exhibit any antagonistic interaction with other classes of antibacterial drugs. 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 hours.

Inhibition of Sporulation of *C. difficile*

Fidaxomicin has been shown to inhibit *C. difficile* sporulation in vitro. Fecal spore counts (CFU count/g) in patients who had received DIFICID® were found to be 2.3 $\log_{10}$ lower at 21 to 28 days post-therapy than in those patients who had received vancomycin.

Suppression of *C. difficile* Toxin Production

Fidaxomicin and OP-1118 suppress the production of both toxin A and toxin B at sub-MIC concentrations and inhibit toxin gene expression in vitro. This suppression continues through one week of culture.

Susceptibility Testing

Fidaxomicin is a topically active drug. In vitro susceptibility test interpretive criteria have not been established because there was no correlation identified between clinical success and the MIC of fidaxomicin needed to inhibit the growth of *C. difficile* isolates. An in vitro MIC susceptibility quality control range was developed so that laboratories that wish to determine the MIC can do so.

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 (3). 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* isolate 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 8.

Table 8 - Acceptable quality control ranges for fidaxomicin

Microorganism	MIC Range (µg/mL)
C. difficile (ATCC 700057)	0.06 – 0.25

TOXICOLOGY

Single-dose toxicity, repeat-dose toxicity, genotoxicity and reproductive toxicity studies were conducted to investigate the toxicity of fidaxomicin. The studies are briefly summarized in Tables 9, 10, and 11. Studies conducted specifically with the major metabolite OP-1118 are summarized in Table 12.

Table 9 - Single-Dose Toxicity

Species/Strain/No. Per Group	Route	Duration of Dosing	Nominal Dose (mg/kg)[a]	Principal Effects Observed
Rat/Crl:CD®(SD)(IGS) BR (5/sex/dose)	Oral (gavage)	Single dose	0, 167, 500, 1000 (vehicle: Labrasol®)	No mortality. **Clinical Signs:** *167 mg/kg:* hair loss on forelegs; few or no feces, colored material around nose and eyes. *167 and 500 mg/kg:* yellow (concentrated) urine. ≥ *167 mg/kg:* staining of fur. **Conclusions:** The clinical signs noted above were not necessarily considered related to fidaxomicin due to the absence of an apparent dose-relationship.
Rat/Crl:CD®(SD)(IGS) BR (5-6/sex/dose)	i.v.	Single dose	0, 20, 62.5, 200 (vehicle: 10% dimethyl acetamide, 20% ethanol, 70% PEG 400)	**Mortality:** *200 mg/kg:* 3 M, 2 F. **Clinical Signs:** *0-62.5 mg/kg:* sore on tail (slight to moderate); discolored urine (red, red/brown, red/yellow). ≥ *62.5 mg/kg:* anogenital staining, tail changes (biting slight to moderate/severe sore); bright yellow urine. *200 mg/kg:* labored breathing, hunched posture, cold to touch, tail changes (blue or black in color, end missing). **Conclusions:** The effects noted in this study occurred at high plasma concentrations, exceeding the therapeutic plasma exposures of the drug. Fidaxomicin at 200 mg/kg (i.v.) resulted in mortality, likely due to the poor solubility and precipitation of fidaxomicin in the vasculature at high plasma concentrations.
Dog/Beagle (3/sex) (non-GLP)	Oral (gavage)	Escalating dose	10, 30, 120[b] (vehicle: LT-2)[c] Each dose was separated by a 7-Day wash out period.	No mortality. **Clinical Signs[d]:** ≥ *10 mg/kg:* abnormal excreta (soft feces, mucoid feces and/or diarrhea); excessive salivation, emesis. **Food Consumption:** ≥ *10 mg/kg:* decreases occurred on Days 0-1. **Conclusions:** Fidaxomicin at single oral doses up to 120 mg/kg was relatively well tolerated under the conditions tested.

Species/Strain/No. Per Group	Route	Duration of Dosing	Nominal Dose (mg/kg)[a]	Principal Effects Observed
Dog/Beagle (2/sex) (non-GLP)	i.v.	Escalating dose	1, 4, 7.5 0.93, 3.7, <u>7.0</u> (corrected intended dose) (vehicle: 1% Solutol® HS-15 in PBS) Each dose was separated by a 7-Day washout period.	No mortality. **Clinical Signs[d]:** *1 mg/kg:* mucoid feces, swelling, skin warm to touch, discolored skin. ≥ *1 mg/kg:* decreased activity. *4 mg/kg:* difficult breathing. ≥ *4 mg/kg:* salivation, tremors. *7.5 mg/kg:* lacrimation, stereotypy, discolored skin. **Conclusions:** Despite the clinical observations, the doses tested were relatively well tolerated under the conditions tested.

[a] Unless otherwise specified, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

[b] Initially, study was designed with 3 escalating doses of 30, 120, and 360 mg/kg at 3 mL/kg. Emesis occurred in all dogs at the first dose of 30 mg/kg (3 mL/kg; 10 mg/mL), thus the dosing volume and each dose was decreased such that the dose volume was 1 ml/kg and the doses were 10, 30, and 120 mg/kg (10, 30, 120 mg/mL).

[c] A self-emulsifying drug delivery system composed of Labrafac WL1349 (9.16%), Labrasol® (24.27%), Labrafil M1944CS (13.65%), Tween-80 (32.92%), Plurol Oleique CC497 (10.0%), Purified Water (10.0%).

[d] It was not possible to conclusively determine whether these effects were test-article related as a comparison to a vehicle control was not part of the study design.

F – Female; i.v. – Intravenous; M – Male; PBS – Phosphate buffered saline; PEG – Polyethylene glycol.

Table 10 - Repeat-Dose Toxicity

Species/Strain/No. Per Group	Route	Duration of Dosing	Nominal Dose (mg/kg)[a]	Principal Effects Observed
Rat/Crl:CD®(SD) (3/sex/dose) (non-GLP)	i.v.	14 days	0, 4 (nominal) 0, 0.45 to 1.1 (actual) (vehicle: 0.2% Tween 80/sterile 5% dextrose)	**Mortality:** One control M died on Day 12. **Organ Weights:** Minimal increases in thymus weights at 15-18% above controls. **Conclusions:** Fidaxomicin was relatively well tolerated under the conditions tested.
Rat/Crl:CD®(SD)(IGS) BR) (10/sex/dose)	Oral (gavage)	28 days	0, 10, 30, 90 (vehicle: Labrasol®)	**Mortality:** Two control F died on Day 4. **Clinical Observations:** *90 mg/kg:* mean body weight gain decreased in M (2 out of 10 rats); thymus organ weights decreased in M; one M had enlarged cecum. **Conclusions:** Fidaxomicin was relatively well tolerated under the conditions tested.
Dog/Beagle (2/sex/dose) (non-GLP)	Oral (capsule)	14 days	0, 2, 5, 16 tablets/day (in gelatin capsules; 200 mg/tablet)[b]	No apparent treatment-related clinical signs or changes.
Dog/Beagle (2/sex/dose) (non-GLP)	Oral (capsule)	14 days	0, 32, 48 tablets/day (in gelatin capsules; 200 mg/tablet)[c]	No mortality. **Clinical Observations:** ≥ *32 tablets/day:* pale feces, soft feces, yellow feces. Emesis containing food, white material, capsule material, or tablet material. Food consumption slightly lower for both M and F. **Conclusions:** Fidaxomicin was relatively well tolerated under the conditions tested.

Species/Strain/No. Per Group	Route	Duration of Dosing	Nominal Dose (mg/kg)[a]	Principal Effects Observed
Dog/Beagle (3/sex/dose)	Oral (gavage)	14 days	0, 30, 60, 120 (vehicle: LT-2)[d]	No mortality. **Clinical Signs:** ≥ *60 mg/kg/day:* abnormal excreta (soft feces, mucoid feces, feces containing white material and/or diarrhea) and/or emesis. **Conclusions:** Fidaxomicin was relatively well tolerated under the conditions tested.
Dog/Beagle (4-7/sex/dose)	Oral (gavage)	2 weeks (Originally planned for 3 months but shortened to 14-15 days due to anaphylactoid reactions)	0, 10, 30, 120 (vehicle: LT-2)[d] NOAEL: ND	Anaphylactoid reactions noted, during the first two weeks of dosing, in 1 animal in the control group, 3 animals in the 10 mg/kg/day group, and 2 animals in the 120 mg/kg/day group were either euthanized in extremis or found dead. Symptoms of the anaphylactoid reactions included facial swelling, low blood pressure, labored respiration, reddening of the skin, hives, and decreased body temperature. Macroscopic findings for animals either euthanized in extremis or found dead included reddening of mucosa of duodenum, ileum, jejunum, colon, cecum, and rectum, and dark red discoloration of the lungs and lymph nodes. **Clinical Signs:** *120 mg/kg/day:* soft feces, mucoid feces, and diarrhea; emesis containing white material. **Conclusions:** Due to the anaphylactoid reactions in the control group and test article-treated group animals, the study was terminated on Study Day 20.
Dog/Beagle (4-7/sex/dose)[e]	Oral (capsule)	3 months	0, 5, 16, 48 tablets/day (in gelatin capsules; 200 mg/tablet)[f]	No mortality. **Clinical Observations:** Pale/yellow feces and feces containing white/yellow material in all fidaxomicin-treated groups; emesis of white material in all groups including control but increased particularly in the high dose group. **Conclusions:** Effects of fidaxomicin appear to have been limited to gastrointestinal effects, as evidenced by clinical observations of pale/yellow feces and white emesis.

Species/Strain/No. Per Group	Route	Duration of Dosing	Nominal Dose (mg/kg)[a]	Principal Effects Observed
Monkey/Cynomolgus (3/sex/dose)	Oral (gavage)	28 days	0, 10, 30, 90 (nominal) 0, 11.3, 33.9, <u>101.7</u> (actual) (vehicle: Labrasol®)	Procedure-related accidental death (gavage-related trauma) occurred in two 90 mg/kg/day treated monkeys (1 M and 1 F). Findings included severe hypoactivity, hypothermia, red material on mouth and nose, ptosis and palor, presence of red foamy material in the trachea, multiple areas of dark discoloration on all lobes of the lungs. **Conclusions:** Oral administration of fidaxomicin for 28 days to Cynomolgus monkeys was well tolerated.

[a] Unless otherwise specified, the highest No Observed Adverse Effect Level (NOAEL) is underlined.
[b] Animals were given 0, 400, 1000, 3200 mg/day.
[c] Animals were given 0, 6400, 9600 mg/day.
[d] A self-emulsifying drug delivery system composed of Labrafac WL1349 (9.16%), Labrasol® (24.27%), Labrafil M1944CS (13.65%), Tween-80 (32.92%), Plurol Oleique CC497 (10.0%), Purified Water (10.0%).
[e] The control and 48 tablets/day groups each consisted of 7 males and 7 females, and the 5 and 16 tablets/day groups each consisted of 4 males and 4 females. Four animals/sex/group were scheduled for the primary necropsy at the end of the 91-day treatment period. The remaining 3 animals/sex in the control and 48 tablet/day groups were assigned to a 28-day recovery period.
[f] Animals were given 0, 1000, 3200, 9600 mg/day.

F – Female; i.v. – Intravenous; M – Male; ND – not determined; NOAEL – No Observed Adverse Effect Level; PEG – Polyethylene glycol.

Table 11 - Genotoxicity

Type of Study	Route	Duration of Dosing	Nominal Dose	Principal Effects Observed
Ames Assay/*S. typhimurium* and *E. coli*	In vitro	48-72 hour incubation (+/- S9)	*Fidaxomicin* Initial: 1.5-5000 µg/plate Confirmatory: 50-5000 µg/plate (vehicle: DMSO)	Under the conditions tested, fidaxomicin did not cause a mutagenic response when tested in the Bacterial Reverse Mutation Assay in the absence or presence of S9.
Ames Assay/*S. typhimurium* and *E. coli*	In vitro	48-72 hour incubation (+/- S9)	*Aged Fidaxomicin* Initial: 0.015-5000 µg/plate Confirmatory: 50-5000µg/plate[a] (vehicle: DMSO)	Under the conditions tested, aged fidaxomicin (lot aged 3.5 years) did not cause a mutagenic response when tested in the Bacterial Reverse Mutation Assay in the absence or presence of S9.

Type of Study	Route	Duration of Dosing	Nominal Dose	Principal Effects Observed
Mammalian Chromosomal Aberration Test/Chinese hamster ovary (CHO) cells	In vitro	4 hour exposure (+/- S9) 20 hour exposure (- S9)	*Fidaxomicin* First experiment 12.5-200 µg/mL (-S9; 4 and 20 hr exposures) 3.125-100 µg/mL (+S9; 4 hr exposure) Repeat assay 50-140 µg/mL (-S9; 4 hr exposure) 3.125-150 µg/mL (+S9; 4 hr exposure)	**Cytotoxic Effects:** Substantial toxicity was noted at ≥ 240 µg/mL (4 hr, -S9) and at ≥ 80 µg/mL (4 hr, +S9 and 20 hr, -S9). **Genotoxic Effects:** Fidaxomicin was positive for the induction of structural chromosome aberrations without S9 in CHO cells. Fidaxomicin was negative for the induction of structural chromosome aberrations with S9 and negative for the induction of numerical chromosome aberrations in CHO cells.
Mammalian Erythrocyte Micronucleus Test/Rat/ Sprague Dawley (5 M/dose)	i.v.	Single dose	*Fidaxomicin* 24 hr: 0, 18.75, 37.5, 75 48 hr: 0, 75 mg/kg (vehicle: 10% dimethyl acetamide/20% ethanol/70% PEG 400)	A statistically significant increase in MPCEs was observed in the 37.5 mg/kg fidaxomicin group 24 hours post-dose relative to the control group ($p \leq 0.05$). However, the number of MPCEs in male rats in this group appeared to be within the range of historical control values and was not considered to be biologically significant.
Comet Assay/Rat/ Sprague Dawley (6 M/dose)	Oral	2 days (fidaxomicin and vehicle) Single dose (EMS, positive control)	*Aged Fidaxomicin* 0, 500, 1000, 2000 mg/kg (vehicle: Labrasol®) *Ethyl methanesulfonate (EMS)* 200 mg/kg	Some of the animals at 2000 mg/kg/day were lethargic prior to (3/6) and after (5/6) dosing on study Day 2. Under the conditions tested, fidaxomicin at oral doses up to 2000 mg/kg/day, did not appear to cause an increase in DNA damage in liver or duodenal cells relative to the concurrent vehicle controls in male rats. A dose-dependent decrease in % tail DNA (DNA damage) in duodenal cells was observed (regression analysis, $p \leq 0.05$), though the mean values in the test article groups did not appear to significantly differ relative to the concurrent negative (vehicle) control group. The biological significance is uncertain.

[a] Fidaxomicin test concentrations range for nonactivated TA100 was extended to 15-5000 µg/plate.

CHO – Chinese hamster ovary; DMSO – dimethylsulfoxide; EMS – Ethyl methanesulfonate (positive control); hr – hour; i.v. – Intravenous; M – Male; MPCE – micronucleated polychromatic erythrocytes; PEG – Polyethylene glycol.

Table 12 - Other Toxicity Studies (Studies with OP-1118 – Main Metabolite of Fidaxomicin)

Type of Study	Route	Duration of Dosing	Nominal Dose	Principal Effects Observed
Ames Assay/*S. typhimurium* and *E. coli*	In vitro	48-72 hour incubation (+/- S9)	*OP-1118* Initial: 1.5-5000 µg/plate Confirmatory: 50-5000 µg/plate (vehicle: DMSO)	Under the conditions tested, OP-1118 did not cause a mutagenic response when tested in the Bacterial Reverse Mutation Assay in the absence or presence of S9.
Mammalian Chromosomal Aberration Test/Chinese hamster ovary (CHO) cells	In vitro	4 hour exposure (+/- S9) 20 hour exposure (- S9)	*OP-1118* 500-4000 µg/mL (-S9; 4 hr exposure) 100-1200 µg/mL (+S9; 4 hr exposure and -S9; 20 hr exposure) (vehicle: DMSO)	**Cytotoxic Effects:** Substantial toxicity was noted at 5000 µg/mL (4 hr, -S9) and at ≥ 1500 µg/mL (4 hr, +S9 and 20 hr, -S9). **Genotoxic Effects:** With a 4 hour treatment in the presence of S9 fraction, the 900 µg/mL OP-1118 group showed a slight increase in the percentage of cells with numerical and structural aberrations. Similar results were seen with a 20 hour treatment without metabolic activation. The percentage of cells with numerical aberrations in the non-activated 20-hour exposure group was statistically increased relative to solvent control at 900 µg/mL OP-1118 ($p \leq 0.05$). The Cochran-Armitage test was also positive for a dose response. However, the percentage of cells with numerical aberrations (2.5%) appeared to be within the range of historical control range (0-7.5%). The biological significance is uncertain.

CHO – Chinese hamster ovary; DMSO – dimethylsulfoxide; hr – hour.

Carcinogenicity
Long-term animal carcinogenicity studies were not conducted for fidaxomicin.

Reproductive and Developmental Toxicity
Reproductive toxicity studies were conducted in rats (1 to 15 mg/kg fidaxomicin, i.v.) and rabbits (1 to 7.5 mg/kg fidaxomicin, i.v.) in order to assess the effect of fidaxomicin on fertility and embryonic development. In order to maximize systemic exposure, fidaxomicin was delivered i.v. in these studies using an aqueous vehicle, 1% Solutol® HS-15/PBS.

Fidaxomicin at the highest dose tested in rats and rabbits had no maternal, reproductive or embryo-fetal developmental toxicity, or fertility effects. Thus, the NOEL in these species was 15 mg/kg/day in rats and 7.5 mg/kg/day in rabbits. The plasma exposures (AUC_{0-t}) in rats and rabbits at these doses were approximately 200- and 66-fold over human exposure at the therapeutic dose level, respectively.

Local Tolerance
Local tolerance studies were not conducted for fidaxomicin.

REFERENCES

1) Louie TJ, Miller MA, Mullane KM, Weiss K, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364(5):422-31.

2) Cornely AW, Crook DW, Esposito R, Poirier A, Somero MS, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. The Lancet Infect Dis. 2012;12(4):281-289.

3) 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, PA19087-1898, 2007.

PART III: CONSUMER INFORMATION

PrDIFICID®
(fidaxomicin)

This leaflet is part III of a three-part "Product Monograph" published when DIFICID® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DIFICID®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DIFICID® is used in adults to treat infections of the lining of the colon (large intestine) with certain bacteria called *Clostridium difficile*. This serious illness can result in painful, severe diarrhea.

Antibacterial drugs like DIFICID® treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, DIFICID® should be used exactly as directed. Misuse or overuse of DIFICID® could lead to the growth of bacteria that will not be killed by DIFICID® (resistance). This means that DIFICID® may not work for you in the future. Do not share your medicine.

What it does:
DIFICID® is used to kill the bacteria which cause *Clostridium difficile* infections.

When it should not be used:
If you are allergic (hypersensitive) to the active substance fidaxomicin, or any of the other ingredients of DIFICID® (see **What the nonmedicinal ingredients are**).

What the medicinal ingredient is:
fidaxomicin

What the nonmedicinal ingredients are:
butylated hydroxytoluene, hydroxypropyl cellulose, lecithin (soy), magnesium stearate , microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinised starch, sodium starch glycolate, talc and titanium dioxide.

What dosage forms it comes in:
Tablets: 200 mg

WARNINGS AND PRECAUTIONS

BEFORE you use DIFICID® talk to your doctor or pharmacist:

- If you have severe kidney problems or severe liver problems
- If you have inflammatory bowel disease
- If you have any allergies to this drug or its ingredients or components of the container
- If you have a known allergy to other antibiotics
- If you are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine. You should not take DIFICID® if you are pregnant, unless your doctor tells you otherwise.
- If you are breastfeeding ask your doctor or pharmacist for advice before taking this medicine. It is not known whether fidaxomicin passes into breast milk.
- DIFICID® should not be used in children or adolescents less than 18 years of age, as there is no information on the use in that population.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

PROPER USE OF THIS MEDICATION

Usual adult dose:
The recommended dose is one tablet (200 mg) twice daily (one tablet every 12 hours) for 10 days.

Swallow the tablets whole with a glass of water. You can take DIFICID® before, during or after meals.

Full course of medication should be completed as prescribed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Take the tablet as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them.

DIFICID® may cause the following side effects:

- nausea, constipation, vomiting
- decreased appetite
- dizziness, headache
- dry mouth, altered taste (dysgeusia)
- bloated feeling, wind (flatulence)

DIFICID® can cause abnormal blood test results (i.e., increased or abnormal liver enzymes). Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Rare	**Severe Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

This is not a complete list of side effects. For any unexpected effects while taking DIFICID®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

DIFICID® should be stored at room temperature (15° to 30°C) in a tightly closed container away from heat and direct light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about DIFICID®**:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or www.merck.ca or by calling 1-800-567-2594.

To report an adverse event related to DIFICID®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last revised: January 29, 2018

®Optimer Pharmaceuticals, Inc. Used under license.