PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDIFICID®

fidaxomicin

Film-coated tablet, 200 mg, oral

Antibacterial agent

Merck Canada Inc.

16750 route Transcanadienne

Kirkland, QC H9H 4M7

www.merck.ca

Date of Revision:
March 29, 2019

Submission Control No: **215516**
Internal Filing – Revision date: April 4, 2023

RECENT MAJOR LABEL CHANGES

Warnings and Precautions, (7.1, 7.1.1), April 2018

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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*.

1.1 Pediatrics

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

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

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

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

3.2 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.

No dose adjustment in adults is necessary based on age or gender. No dose adjustment is

recommended based on renal function or hepatic impairment.

Pediatrics <18 years of age: The safety and efficacy of DIFICID® in patients below18 years of age have not been established.

Geriatrics ≥65 years of age: No dose adjustment is recommended for elderly patients.

3.3 Administration
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.

3.4 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.

4 OVERDOSAGE

No cases of acute overdose have been reported in humans.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablet/ 200 mg/ fidaxomicin	Tablets: Butylated Hydroxytoluene, Hydroxypropyl Cellulose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinised Starch, Sodium Starch Glycolate Coat: Lecithin (Soy), Polyethylene glycol Polyvinyl Alcohol, Talc, Titanium Dioxide.

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.

6 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 NON-CLINICAL 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.

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
Due to limited clinical data fidaxomicin should be used with caution in patients with moderate to severe hepatic impairment.

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
Due to limited clinical data, fidaxomicin should be used with caution in patients with severe renal impairment.

Susceptibility/Resistance
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.

6.1 Special Populations

6.1.1 Pregnant Women

There are no data available on the use of DIFICID® in pregnant women.

In rats and rabbits there were no maternal or reproductive effects or effects on embryo-fetal development observed at DIFICID® exposures 193-fold higher in rats and 66-fold higher in rabbits, compared to human exposure of DIFICID® at the recommended clinical dose. In the same studies, exposure to the primary metabolite of DIFICID®, OP-1118, was 65-fold higher in rats and 245-fold higher in rabbits compared to human exposure of OP-1118 at the recommended clinical dose of DIFICID®.

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 (See NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity).

6.1.2 Breast-feeding

It is not known whether fidaxomicin and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical needs for DIFICID® and any potential adverse effects on the breastfed child from DIFICID® or from the underlying maternal condition.

6.1.3 Pediatrics

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

6.1.4 Geriatrics

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.

7 ADVERSE REACTIONS

7.1 Adverse 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.

7.2 Clinical Trial Adverse 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 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 2 and the Less Common Clinical Trial Adverse Drug Reactions are presented below the table.

Table 2 - 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)

7.3 Less Common Clinical Trial Adverse Reactions

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

7.4 Post-Market Adverse 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.

8 DRUG INTERACTIONS

8.1 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.

8.2 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 3 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
P-glycoprotein inhibitors			

Proper name	Ref	Effect	Clinical comment
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.
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

8.3 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.

8.4 Drug-Herb Interactions
Drug-Herb interactions have not been studied.

8.5 Drug-Laboratory Test Interactions
Drug-Laboratory test interactions have not been studied.

8.6 Drug-Lifestyle Interactions
Drug-Lifestyle interactions have not been studied.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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**).

9.2 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.

9.3 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 4 below.

Table 4 - 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.

Elimination: 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.

Sex: 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.

Inflammatory bowel disease: The effect of concomitant inflammatory bowel disease (IBD) on the pharmacokinetics of fidaxomicin and OP-1118 was evaluated in an open label, single arm study in CDI patients. No major differences in plasma concentrations of fidaxomicin or its main metabolite OP-1118 was found in patients with IBD as compared with patients without IBD in other studies. Fidaxomicin and OP-1118 plasma levels in CDI patients with concomitant IBD were within the same range of levels found in CDI patients without IBD 1–5 h post-dose on the last day of dosing (day 10).

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.

10 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

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

11 PHARMACEUTICAL INFORMATION

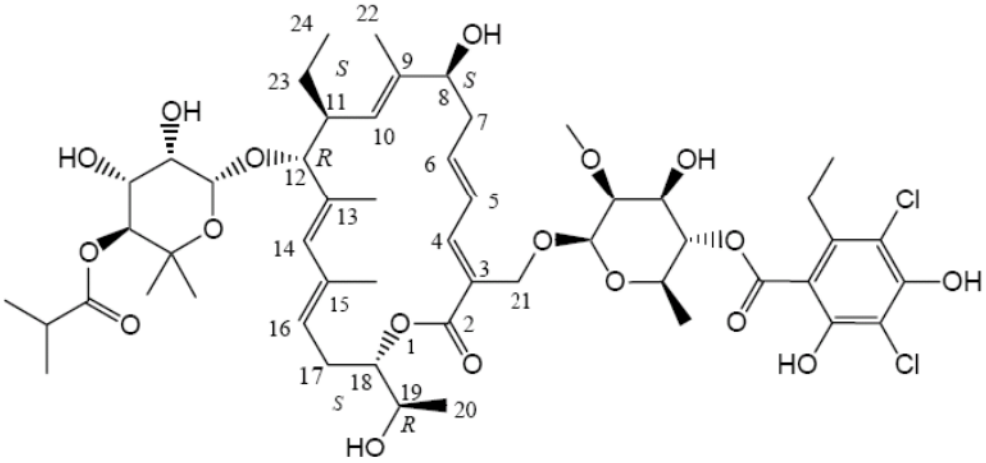
Drug Substance

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)

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

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

Table 5 - 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 (**Error! Reference source not found.**	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 (**Error! Reference source not found.**	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.

12.2 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 6, 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 6 - 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 6, 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 7.

Table 7 - 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 8).

Table 8 - 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).

Safety in patients with moderate or severe hepatic impairment, severe renal impairment and fulminant or life-threatening *C. difficile* infection

In a retrospective post-authorization study, data from 576 patients treated with fidaxomicin for CDI were evaluated. Defined co-morbid conditions of specific medical interest present were moderate or severe hepatic impairment (50 patients), severe renal impairment (104 patients) and fulminant or life-threatening CDI based on the clinical judgment of the investigator (87 patients). Mortality rates were 33.7% (35/104) in severe renal impairment and 20.0% (10/50) in moderate-to-severe hepatic impairment, and 17.2% (5/29) in patients with IBD. In general, the mortality rate was slightly higher in patients with at least one medical condition of interest 28.4% (74/261) than in patients with none 22.9% (72/315). Evaluation of the incidence of mortality, laboratory and ECG data did not indicate additional safety concerns in patients with a medical condition of interest compared with those who did not have any of these conditions.
CDI. Evaluation of the incidence of mortality, laboratory and ECG data did not indicate additional safety concerns in patients with a medical condition of interest compared with those who did not have any of these conditions.

Safety in patients with inflammatory bowel disease

In the retrospective post-authorization study 29 CDI patients with co-morbid IBD were included. The mortality rate in patients with IBD was 17.2% (5/29) and was lower than that of other patients with at least one medical condition of interest. Evaluation of the incidence of mortality, laboratory and ECG data did not indicate additional safety concerns in patients with IBD compared with those who did not have a medical condition of interest.

An open label, single arm, phase IIIB/IV study of fidaxomicin has been conducted to investigate

the plasma PK of fidaxomicin and its main metabolite OP-1118 in CDI subjects with inflammatory bowel disease (IBD). Fourteen patients with Crohn's Disease (CD) and 11 with Ulcerative colitis (UC). Of the 25 subjects enrolled with active IBD, 24 fulfilled the criteria for the PK analysis set. The maximum plasma concentrations of fidaxomicin and its active metabolite OP-1118 in these subjects were within the measured range of concentration values found in earlier studies of fidaxomicin and OP-1118 involving CDI patients without IBD.

13 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-Il43-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 (**Error! Reference source not found.**. 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 9.

Table 9 - Acceptable quality control ranges for fidaxomicin

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

14 NON-CLINICAL 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.

15 NON-CLINICAL TOXICOLOGY

Carcinogenicity
Carcinogenicity studies have not been conducted.

Genotoxicity
DIFICID® and OP-1118 were negative for mutagenic potential in the Ames assay. OP-1118 was negative in the in vitro chromosomal aberration assay in Chinese Hamster Ovary cells. DIFICID® was positive in the in vitro chromosomal aberration assay in Chinese Hamster Ovary cells but negative in the in vivo rat bone marrow micronucleus assay and the in vivo DNA damage Comet assay in rat liver and duodenum at exposures higher than the human exposure at the recommended clinical dose. The weight of evidence supports that DIFICID® is not genotoxic in vivo and does not represent a risk of genotoxicity in clinical use.

Reproduction

Fertility
A rat study was conducted to assess mating, fertility, and early embryonic development (through implantation). Male and female rats were dosed intravenously with either 1, 4, and 7.5 mg/kg/day, with male rats dosed daily beginning 28 days prior to mating, through mating to Day 28 post-mating (a total of 56 days) and female rats dosed daily beginning 14 days prior to mating, through mating to gestation Day 7 (a total of 21 days). No effects on mating, on male or female fertility, or on early embryonic development were observed in rats at DIFICID® exposures up to 98-fold higher in male rats and 105-fold higher in female rats compared to human exposure at the recommended clinical dose.

Pregnancy
Maternal, reproductive and embryo-fetal effects were assessed in pregnant rats administered daily intravenous DIFICID® doses of 4, 8, and 15 mg/kg from gestation Days 6 through 17 and in pregnant rabbits administered daily intravenous DIFICID® doses of 2, 4, and 7.5 mg/kg from gestation Days 6 through 18. No maternal effects or effects on reproductive or embryo-fetal development were observed at DIFICID® exposures 193-fold higher in rats and 66-fold higher in rabbits, and at exposures of the primary metabolite of DIFICID®, OP-1118, that were 65-fold higher in rats and 245-fold higher in rabbits compared to human exposure at the recommended clinical dose.

Development
DIFICID® did not have any effects on the juvenile dog when orally administered daily for 4-weeks at up to 200 mg/kg, the highest dose tested. The exposures to DIFICID® and the primary metabolite of DIFICID®, OP-1118, were approximately 21- and 0.8-fold, respectively, the exposure in humans at the recommended clinical dose.

Local Tolerance
Local tolerance studies were not conducted for fidaxomicin.
Narrative where possible. Include a table only where presentation is made more concise.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrDIFICID®

(fidaxomicin)

Read this carefully before you start taking **DIFICID®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DIFICID®**.

What is DIFICID® used for?

DIFICID® is used in adults to treat colon (large intestine) infections that are caused by 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.

How does DIFICID® work?

DIFICID® contains an antibiotic that reduces infections by:

- Stopping the growth of bacteria.
- Killing bacteria.

What are the ingredients in DIFICID®?

Medicinal ingredients: fidaxomicin

Non-medicinal ingredients: butylated hydroxytoluene, hydroxypropyl cellulose, lecithin (soy), magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinised starch, sodium starch glycolate, talc and titanium dioxide.

DIFICID® comes in the following dosage forms:

Tablets: 200 mg

Do not use DIFICID® if:

If you are allergic (hypersensitive) to fidaxomicin, or any of the other ingredients of DIFICID®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DIFICID®. Talk about any health conditions or problems you may have, including if you:

- Have a known allergy to other antibiotics.
- Have had a previous gut infection (such as *Clostridium difficile*).
- 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.
- Are breastfeeding ask your doctor or pharmacist for advice before taking this medicine. It is not known whether fidaxomicin passes into breast milk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take DIFICID®:

- 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.
- Swallow the tablets whole with a glass of water. You can take DIFICID® with or without food.

Usual dose:
One tablet (200 mg) every 12 hours for 10 days.

Overdose:

If you think you have taken too much DIFICID®, contact your healthcare professional, 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.

What are possible side effects from using DIFICID®?

These are not all the possible side effects you may feel when taking DIFICID®. If you experience any side effects not listed here, contact your healthcare professional.

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 and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get 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			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:
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".

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.

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 Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.merck.ca or by calling 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last Revised: April 4, 2023