

DIFICID®

NAME OF THE MEDICINE

Active ingredient: fidaxomicin

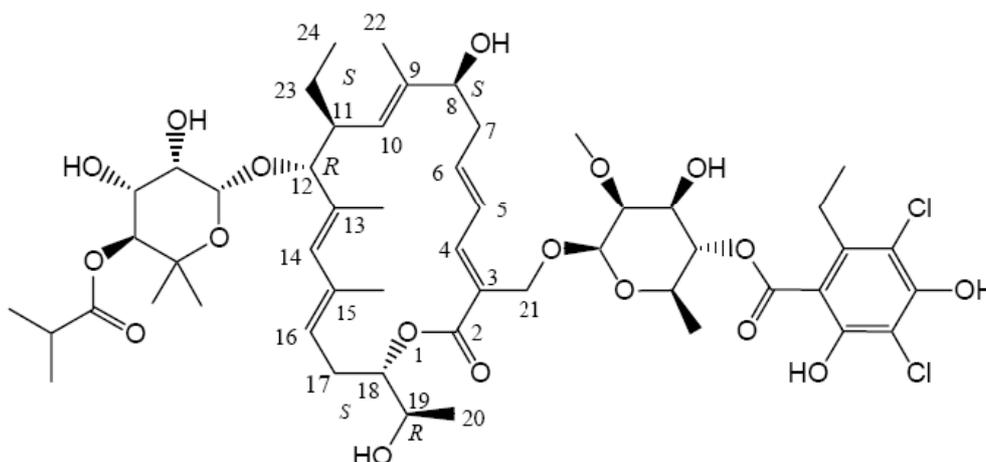
Chemical name: Oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl]oxy]methyl]-12-[[[6-deoxy-5-*C*-methyl-4-*O*-(2-methyl-1-oxopropyl)-β-D-lyxo-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-.

CAS number: 873857-62-6

Molecular weight: 1058.04

Molecular formula: C₅₂H₇₄Cl₂O₁₈

Chemical structure:



DESCRIPTION

Fidaxomicin is the active ingredient in DIFICID. 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. Fidaxomicin is freely soluble in tetrahydrofuran, dimethyl sulfoxide and methanol, soluble in acetone and sparingly soluble in ethyl acetate, ethanol (200 proof), dichloromethane and acetonitrile, and slightly soluble in isopropanol and practically insoluble in water.

List of Excipients

Microcrystalline cellulose, pregelatinised maize starch, hydroxypropylcellulose, butylated hydroxytoluene, sodium starch glycollate, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, Macrogol 3350, lecithin (soy)

PHARMACOLOGY

Mechanism of Action

Fidaxomicin is a novel antibiotic agent and the first of a new class of antibacterials called macrocycles. Fidaxomicin is bactericidal against *Clostridium difficile* (*C. difficile*) *in vitro*, inhibiting RNA synthesis by RNA polymerases. It interferes with RNA polymerase at a site distinct from that of rifamycins.

Fidaxomicin has also been shown to inhibit *C. difficile* sporulation *in vitro*. Faecal spore counts (CFU count/g) in subjects who had received DIFICID were found to be 2.3 log₁₀ lower at 21 to 28 days post-therapy than in those subjects who had received vancomycin.

Microbiology

Antimicrobial spectrum

Fidaxomicin is a narrow spectrum antimicrobial drug with bactericidal activity against *C. difficile*. Fidaxomicin has an MIC₉₀ of 0.25 µg/mL versus *C. difficile*, and its main metabolite, OP-1118, has an MIC₉₀ of 8 µg/mL. Gram negative organisms are intrinsically not susceptible to fidaxomicin.

Inhibition of the Clostridial RNA polymerase enzyme occurs at a concentration that is 20-fold lower than that for the *E. coli* enzyme (1 µM vs. 20 µM), partly explaining the significant specificity of fidaxomicin activity.

Resistance

No cross-resistance has been discovered with any other antibiotic class including β-lactams, macrolides, metronidazole, quinolones, rifampin, and vancomycin. Specific mutations of RNA polymerase are associated with reduced susceptibility to fidaxomicin.

Breakpoints

Fidaxomicin is a topically acting drug that cannot be used to treat systemic infections; therefore the establishment of a clinical breakpoint is not relevant. The epidemiological cut-off value for fidaxomicin and *C. difficile*, distinguishing the wild-type population from isolates with acquired resistance traits, is > 1.0 mg/L.

Mechanism of decreased susceptibility to DIFICID

In vitro studies indicate a low frequency of spontaneous resistance to DIFICID in *C. difficile* (ranging from $<1.4 \times 10^{-9}$ to 12.8×10^{-9}). A specific mutation (Val-1143-Gly) in the beta subunit of RNA polymerase is associated with reduced susceptibility to DIFICID. This mutation was created in the laboratory and seen during clinical trials in a *C. difficile* isolate obtained from a subject treated with DIFICID who had recurrence of CDAD. The *C. difficile* isolate from the treated subject went from a DIFICID baseline minimal inhibitory concentration (MIC) of 0.06 µg/mL to 16 µg/mL.

Cross-Resistance/synergy/post-antibiotic effect

DIFICID and its main metabolite OP-1118 do not exhibit any antagonistic interaction with other classes of antibacterial drugs. *In vitro* synergistic interactions of DIFICID and OP-1118 have been

DIFICID (fidaxomicin) 200 mg Tablets

observed in vitro with rifampin and rifaximin against *C. difficile* (FIC values ≤ 0.5). DIFICID demonstrates a post-antibiotic effect vs. *C. difficile* of 6 – 10 hrs.

Susceptibility Testing

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

Dilution Techniques

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

Susceptibility test Interpretive Criteria

In vitro susceptibility test interpretive criteria for DIFICID have not been determined. The relation of the in vitro DIFICID MIC to clinical efficacy of DIFICID 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 DIFICID so that laboratories determining the susceptibility of *C. difficile* isolate to DIFICID 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 DIFICID powder should provide the MIC with the indicated quality control strain shown below:

Acceptable quality control ranges for Fidaxomicin:

| Microorganism | MIC Range ($\mu\text{g/mL}$) |
|-----------------------------------|--------------------------------|
| <i>C. difficile</i> (ATCC 700057) | 0.03 – 0.25 |

Pharmacodynamics

Fidaxomicin acts locally in the gastrointestinal tract on *C. difficile* with minimal systemic absorption and faecal concentrations in the colon that exceed the MIC₉₀ 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.

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In a clinical study, DIFICID predominantly affected faecal concentrations of *C. difficile* with little to no effect on normal microflora such as *Bacteroides* and other major phylogenetic groups. This characteristic may explain the lower *C. difficile* recurrence rate observed in subjects treated with DIFICID compared to vancomycin. Acquisition of vancomycin-resistant *Enterococcus* (VRE) faecal colonisation is also significantly less frequent in CDI subjects treated with DIFICID than in those treated with vancomycin.

Fidaxomicin has a prolonged *in vitro* post-antibiotic effect (approximately 6 to 10 hours), allowing for twice daily dosing. In a dose-ranging trial of fidaxomicin using 50 mg, 100 mg, and 200 mg twice daily for 10 days, a dose-response relationship was observed for efficacy.

Pharmacokinetics

The pharmacokinetic parameters of fidaxomicin and its main metabolite OP-1118 in plasma following a single oral dose of 200 mg in healthy adult males (N=14) are summarised in Table 1 below.

Table 1 - Mean (\pm Standard Deviation) Pharmacokinetic Parameters of Fidaxomicin and OP-1118 in Healthy Adult Males Following a Single 200 mg Dose

| | C_{max} (ng/mL) | AUC_{0-∞} (ng-hr/mL) | T_{max} (hr)* | t_{1/2} (hr) |
|--------------------|--|---|-------------------------------|-----------------------------|
| Fidaxomicin | 5.20 \pm 2.81 (n=14) | 62.9 \pm 19.5 (n=9) | 2.00 (1.00-5.00) (n=14) | 11.7 \pm 4.80 (n=9) |
| OP-1118 | 12.0 \pm 6.06 (n=14) | 118 \pm 43.3 (n=10) | 1.02 (1.00-5.00) (n=14) | 11.2 \pm 3.01 (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-∞}, 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 subjects 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.

Distribution: Fidaxomicin is mainly confined to the gastrointestinal tract following oral administration. In subjects with CDI treated with DIFICID 200 mg twice daily for 10 days from controlled trials, faecal concentrations of fidaxomicin and OP-1118 obtained within 24 hours of the last dose ranged from 5.0-7630.0 μ g/g and 63.4-4170.0 μ g/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.

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

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

Excretion: Fidaxomicin is mainly excreted in faeces. In one trial of healthy adults (N=11), more than 92% of the dose was recovered in the stool as fidaxomicin and OP-1118 following single doses of 200 mg and 300 mg. In another trial of healthy adults (N=6), <1% of the dose was recovered in urine as OP-1118 only following a single dose of 200 mg.

CLINICAL TRIALS

DIFICID was studied for the treatment of *C. difficile* infection (CDI) in 2 randomised studies.

Table 2 - Summary of Subject Demographics for Clinical Trials in the Treatment of *C. difficile* Infection

| Study | Trial Design | Dosage | Study Subjects (n=number) | Mean Age (Range) |
|--------------|--|---|----------------------------------|-------------------------|
| 101.1.C.003 | Multi-National, Multi-Center, Double-Blind, 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) |
| 101.1.C.004 | Multi-National, Multi-Center, Double-Blind, 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) |

In two multi-national randomised, double-blinded studies, a non-inferiority design was utilised to demonstrate the efficacy of DIFICID (200 mg twice daily for 10 days) compared to vancomycin (125 mg four times daily for 10 days) in adults with CDI (also known as *C. difficile*-associated diarrhoea, or CDAD).

Enrolled subjects 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 randomisation, and presence of either *C. difficile* toxin A or B in the stool within 48 hours of randomisation. Enrolled subjects had either no prior CDI history or only one prior CDI episode in the past three months.

Subjects with fulminant colitis and subjects 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 trials. Subjects had a median age of 64 years, were mainly white (90%), female (58%), and inpatients (63%). Almost half of the subjects (49.4%) were aged ≥ 65 years. Concomitant antibiotics were received by 27.5% (275/999) of subjects at some time during the studies and 19.2% (192/999) of subjects received antibiotics concurrently with study drug.

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 diarrhoea or other symptoms such that, in the Investigator's judgment, further CDI treatment was not needed. Additional efficacy endpoints were recurrence and sustained clinical response. Sustained clinical response was evaluated only for subjects 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 30 days beyond the end of therapy.

DIFICID was demonstrated to be at least as effective as vancomycin in treating CDI (non-inferior), defined as clinical response rates at the end of therapy (88.2% vs. 85.7% respectively in study 101.1.C.003; 87.7% vs. 86.7% respectively in study 101.1.C.004). Notably, DIFICID was associated with significantly greater improvements in the rate of sustained clinical response compared to vancomycin (74.4% vs. 64.2%, $p=0.007$ in study 101.1.C.003; 76.7% vs. 63.3%, $p=0.001$ in study 101.1.C.004). Since clinical response rates at the end of therapy and mortality rates were similar for both treatments, superiority in sustained clinical response was due to lower rates of proven or suspected CDI recurrence during the follow-up period, with significantly lower rates of CDI recurrence with DIFICID than with vancomycin (15.7% vs. 25.1%, $p=0.008$ in study 101.1.C.003; 12.6% vs. 27.0%, $p<0.001$ in study 101.1.C.004).

The results for sustained clinical response at 30 days post-therapy, also shown in Table 3, indicate that DIFICID is superior to vancomycin for this endpoint.

Table 3 - Clinical Response Rates and Sustained Clinical Response Rates (30 Days Post-Therapy)

| Study | Clinical Response at End of Therapy | | | Sustained Clinical Response at 30 Days Post-Therapy | | |
|-------------|-------------------------------------|-----------------------|-------------------------|---|-----------------------|----------------------------------|
| | 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.

Proven or suspected CDI recurrence rates 30 days post-therapy for those subjects who were clinical successes at the end of therapy are shown in Table 4. In both studies, the recurrence rate was significantly lower in the DIFICID group compared to the vancomycin group.

Table 4 - Proven or Suspected CDI Recurrence Rates in Phase 3 Studies

| 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

Among subjects who experienced a recurrence of CDI, recurrence occurred later for DIFICID subjects than for vancomycin subjects.

Results for all endpoints were consistent with the primary findings across most subgroups analysed (including age, sex, race, disease severity, use of concomitant antibiotics, and in-patient vs. out-patient status). For initial strain type of CDI, restriction endonuclease analysis was used to identify *C. difficile* baseline isolates in the BI group, isolates associated with increasing rates and severity of CDI in the years prior to the clinical trials. Similar rates of clinical response at the end of therapy and proven or suspected CDI during the follow-up period were seen in DIFICID-treated and vancomycin-treated subjects infected with a BI isolate.

Amongst the per protocol population, in the absence of concomitant antibiotic use, DIFICID and vancomycin were similar in achievement of clinical response by the end of therapy (92.3% vs. 92.8%; p=0.80). However, when subjects received one or more antibiotics concurrently with study drug, DIFICID was superior to vancomycin in achieving clinical response (90.0% vs. 79.4%; p=0.04). When subjects received no additional antibiotics at any time during the study, the sustained clinical response rate was 80.8% for DIFICID subjects and 69.1% for vancomycin subjects (p<0.001). Sustained clinical response rates were substantially reduced in both treatment groups when subjects received concomitant antibiotics, but significantly more DIFICID subjects achieved sustained clinical response compared to vancomycin (72.7% vs. 59.4%, p=0.02).

A study of subjects treated with DIFICID demonstrated that concentrations of *Bacteroides* or other major phylogenetic groups in the faeces were left unaffected. This sparing effect of the microflora may explain the lower *C. difficile* recurrence rate that was observed in subjects treated with DIFICID compared to vancomycin. Acquisition of vancomycin-resistant *Enterococcus* (VRE) faecal colonisation was significantly less frequent in CDI subjects treated with DIFICID compared to those treated with vancomycin (7% vs. 31%; p<0.001).

INDICATION

DIFICID (fidaxomicin) is indicated for the treatment of confirmed *Clostridium difficile* infection (CDI) in adults.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

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 animal carcinogenicity studies were not conducted for fidaxomicin. Fidaxomicin was clastogenic *in vitro* (Chinese Hamster Ovary Cells, chromosomal aberration test) which is not thought to be clinically relevant. However, fidaxomicin was not genotoxic in assays of bacterial mutagenicity, or *in vivo* clastogenicity (rat bone marrow micronucleus test) and liver and duodenal DNA damage (rat comet assay). Based on data from animal studies, fidaxomicin is not expected to be genotoxic in humans.

Cardiovascular

Electrocardiogram (ECG) parameters and QT intervals (QTc) were measured in subjects participating in clinical 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.

Hypersensitivity reactions

Acute hypersensitivity reactions, such as dyspnoea, 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.

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 reactions.

Hepatic/Biliary/Pancreatic

There are limited clinical data in subjects with severe hepatic insufficiency. Therefore, DIFICID should be used with caution in such patients.

Renal

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

Effects on Fertility

Male and female fertility were unaffected in rats dosed intravenously with up to 6.3 mg/kg/day fidaxomicin, for at least two weeks prior to and throughout mating, yielding fidaxomicin plasma AUC levels up to 60-times that of humans at the maximum recommended clinical dose.

Use in Pregnancy (Category B1)

There are no adequate and well-controlled studies 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, administered during the period of organogenesis. The plasma exposures (AUC_{0-t}) at these doses were approximately 200 and 66 fold that in humans, respectively, and have revealed no evidence of harm to the fetus due to fidaxomicin.

Because animal reproduction studies are not always predictive of human response, DIFICID should be used during pregnancy only if clearly needed.

Use in Lactation

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

Use in Children

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

Use in Elderly

Of the total number of subjects with CDI enrolled in controlled trials of DIFICID, almost half (272, 48.2%) of the DIFICID-treated subjects were 65 years of age and over. In controlled trials, elderly subjects (≥65 years of age) had higher plasma concentrations of fidaxomicin and its main metabolite, OP-1118, versus non-elderly subjects (<65 years of age). However, the magnitudes of increase in exposures in elderly subjects were not considered to be clinically significant.

No dose adjustment is recommended for elderly patients.

INTERACTIONS WITH OTHER MEDICINES

Overview

No clinically relevant metabolism of fidaxomicin by human cytochrome P450 (CYP) enzymes was observed. Fidaxomicin does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4/5 enzymes *in vitro*. Systemic inhibition of CYP enzymes is not expected due to the low plasma levels after oral dosing. Inhibition of CYP2C9 and CYP3A4/5 in the gastrointestinal tract is possible due to the high concentrations reached locally. No clinically relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1 was observed.

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 (Table 5). 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 the increase is not considered clinically significant as concentrations remained very low (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 subjects with *C. difficile* infection, concomitant P-gp inhibitor use had no attributable effect on safety or treatment outcome of DIFICID-treated subjects. 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 and no dose adjustment is necessary. However, a larger effect on P-gp substrates with lower bioavailability more sensitive to intestinal P-gp inhibition, such as dabigatran etexilate, cannot be excluded.

Table 5 - Established or Potential Drug-Drug Interactions

| Proper Name | Ref | Effect | Clinical Comment |
|----------------------------------|-----|--------------------------------------|---|
| <i>P-glycoprotein inhibitors</i> | | | |
| 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. No dose adjustment is recommended. |
| <i>P-glycoprotein substrates</i> | | | |
| 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. |
| <i>CYP2C9 substrate</i> | | | |
| 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. |
| <i>CYP3A4 substrate</i> | | | |
| 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. |

| <i>CYP2C19 substrate</i> | | | |
|--------------------------|----|-----------|--|
| 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

ADVERSE EFFECTS

Clinical Trial Adverse Effects Overview

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.

In the DIFICID Phase 3 clinical trials, the overall incidence of adverse events was similar for subjects in the DIFICID (68.3%) and vancomycin (65.5%) groups. The overall incidence of mild, moderate, and severe adverse events was similar for the DIFICID and vancomycin groups.

In the Phase 3 clinical trials, the incidence of an adverse event for which drug was stopped permanently or the subject discontinued from the study was low (<10% across treatment groups). 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. Vomiting was the primary adverse event leading to discontinuation of dosing; this occurred at an incidence of 0.5% in both the fidaxomicin and vancomycin subjects in the pooled Phase 3 studies.

Compared to vancomycin, more patients treated with DIFICID experienced neutropenia-related events (2.4% versus 1.0%). However, these events were considered not drug-related by the investigators.

All adverse events that occurred at an incidence $\geq 2\%$ in the Phase 3 clinical trials are provided in Table 6. (These include adverse events that may be attributable to the underlying disease).

Table 6: Summary of Adverse Events with a $\geq 2\%$ Incidence in Any Treatment Group: Phase 3 Studies (Safety Population)

| Preferred Term | Fidaxomicin 400mg (N=564) n (%) | Vancomycin 500mg (N=583) n (%) |
|--|---------------------------------------|--------------------------------------|
| Any Adverse Event | 385 (68.3) | 382 (65.5) |
| Blood and Lymphatic System Disorders | 37 (6.6) | 25 (4.3) |
| Anemia | 14 (2.5) | 12 (2.1) |
| Gastrointestinal Disorders | 177 (31.4) | 170 (29.2) |
| Nausea | 62 (11.0) | 66 (11.3) |
| Vomiting | 41 (7.3) | 37 (6.3) |
| Abdominal pain | 33 (5.9) | 23 (3.9) |
| Diarrhea | 28 (5.0) | 39 (6.7) |
| Constipation | 25 (4.4) | 12 (2.1) |
| Abdominal pain upper | 9 (1.6) | 12 (2.1) |
| General Disorders and Administration Site Conditions | 90 (16.0) | 113 (19.4) |
| Pyrexia | 24 (4.3) | 31 (5.3) |
| Edema peripheral | 20 (3.5) | 27 (4.6) |
| Fatigue | 17 (3.0) | 20 (3.4) |
| Chills | 3 (0.5) | 14 (2.4) |
| Infections and Infestations | 129 (22.9) | 121 (20.8) |
| Urinary tract infection | 20 (3.5) | 24 (4.1) |
| Pneumonia | 13 (2.3) | 18 (3.1) |
| Metabolism and Nutrition Disorders | 104 (18.4) | 87 (14.9) |
| Hypokalemia | 41 (7.3) | 38 (6.5) |
| Hyperkalemia | 16 (2.8) | 10 (1.7) |
| Hypomagnesemia | 8 (1.4) | 12 (2.1) |
| Musculoskeletal and Connective Tissue Disorders | 44 (7.8) | 40 (6.9) |
| Back pain | 8 (1.4) | 13 (2.2) |
| Nervous System Disorders | 71 (12.6) | 64 (11.0) |
| Headache | 37 (6.6) | 27 (4.6) |
| Dizziness | 16 (2.8) | 12 (2.1) |
| Psychiatric Disorders | 41 (7.3) | 44 (7.5) |
| Insomnia | 13 (2.3) | 14 (2.4) |
| Respiratory, Thoracic and Mediastinal Disorders | 63 (11.2) | 76 (13.0) |
| Dyspnea | 14 (2.5) | 13 (2.2) |
| Skin and Subcutaneous Tissue Disorders | 54 (9.6) | 56 (9.6) |
| Pruritus | 10 (1.8) | 14 (2.4) |
| Vascular Disorders | 36 (6.4) | 31 (5.3) |
| Hypotension | 11 (2.0) | 12 (2.1) |

Clinical Trial Adverse Drug Reactions 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.

DIFICID (fidaxomicin) 200 mg Tablets

The following adverse drug reactions were reported in subjects in controlled clinical trials on treatment with DIFICID in more than 1 subject:

| System Organ Class | Common ($\geq 1/100$ to $< 1/10$) | Uncommon ($\geq 1/1000$ to $< 1/100$) |
|------------------------------------|-------------------------------------|---|
| Gastrointestinal Disorders | nausea, constipation, vomiting | abdominal distension, flatulence, dry mouth |
| Metabolism and Nutrition Disorders | | anorexia |
| Nervous System Disorders | | dysgeusia, headache, dizziness |
| Investigations | | alanine aminotransferase increased |

Post-Market Experience

The following adverse reactions have been identified during post approval use of DIFICID. The frequency of these reactions is not known (cannot be estimated from the available data).

Immune System Disorders: hypersensitivity reaction (rash, pruritus, angioedema, dyspnea)

DOSAGE AND ADMINISTRATION

The recommended dose is 200 mg (one tablet) administered twice daily (once every 12 hours) for 10 days.

DIFICID can be taken before, during or after meals.

Adults and elderly (≥ 65 years of age):

No dose adjustment is recommended for elderly patients.

Patients with renal impairment:

No dose adjustment is recommended for patients with renal insufficiency.

Patients with hepatic impairment:

No dose adjustment is recommended for patients with hepatic insufficiency.

Patients undergoing dialysis:

No dose adjustment is recommended for patients undergoing dialysis.

Patients with concomitant disease:

No dose adjustment is recommended for patients with concomitant disease.

Children:

Safety and efficacy of DIFICID in patients under the age of 18 has not been established. Therefore, DIFICID is not recommended for use in children.

OVERDOSAGE

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

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation

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 are supplied as:

- HDPE Bottles containing 20 and 60 tablets and a desiccant and fitted with a child-resistant cap.
- Perforated aluminium foil blisters with a white paper backing. Each blister card contains 10 tablets, The 20 and 100 tablet carton packs contain 2 and 10 blister cards per carton, respectively

Not all packs may be marketed.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

In Australia:

Merck Sharp and Dohme (Australia) Pty Limited

Level 1, Building A, 26 Talavera Road

Macquarie Park NSW 2113

Australia

In New Zealand:

Merck Sharp & Dohme (New Zealand) Ltd

P O Box 99 851

Newmarket

Auckland 1149

DIFICID (fidaxomicin) 200 mg Tablets

New Zealand

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

23 April 2013

DATE OF THE MOST RECENT AMENDMENT

1 June 2015