AUSTRALIAN PI – DIFICID® (FIDAXOMICIN) TABLETS

1 NAME OF THE MEDICINE

fidaxomicin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fidaxomicin is the active ingredient in DIFICID.

Each film-coated tablet contains 200 mg of fidaxomicin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF 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 impairment. Due to the limited clinical data in this population, DIFICID should be used with caution in patients with severe renal impairment (see section 5.2).

Patients with hepatic impairment:

No dose adjustment is recommended for patients with hepatic impairment. Due to the limited clinical data in this population, DIFICID should be used with caution in patients with moderate to severe hepatic impairment (see Section 5.2).

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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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.

Use in the 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)[see section 5.2, Special populations]. 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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Ciclosporin is an inhibitor of multiple transporters, including P-gp. When ciclosporin 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 1 - Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
P-glycoprotein inhibitors			
Ciclosporin	CT	↑ fidaxomicin C_{max}, AUC	Co-administration of single doses of the P-gp inhibitor ciclosporin 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.
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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A rat study was conducted to assess mating, fertility, and early embryonic development (through implantation). Male and female rats were dosed intravenously with up to 6.3 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 fidaxomicin exposures up to approximately 100-fold higher compared to the measured human exposure following a single 200 mg dose, or up to approximately 50-fold higher compared to the estimated exposures at the recommended human dose of 200 mg twice daily.

Use in pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies of DIFICID in pregnant women. Embryo-fetal development 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. There were no maternal toxicity or effects on embryo-fetal development observed at fidaxomicin exposures up to 193-fold higher in rats and 66-fold higher in rabbits and OP-1118 exposures up to 65-fold higher in rats and 245-fold higher in rabbits, compared to human exposures following a single 200 mg dose of fidaxomicin. Estimated exposure multiples at the recommended human dose of 200 mg twice daily are approximately half of the multiples following a single 200 mg dose. Because animal reproduction studies are not always predictive of human response, DIFICID should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in lactation

It is not known whether fidaxomicin and /or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, the development 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of DIFICID on the ability to drive and use machines have been performed. Based on the adverse effects and pharmacokinetic profile of DIFICID, it is not anticipated that the use of this drug will affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 ≥2% in the Phase 3 clinical trials are provided in Table 2. (These include adverse events that may be attributable to the underlying disease).

Table 2: Summary of Adverse Events with a ≥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.

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 (≥1/100 to <1/10)**	**Uncommon (≥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)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 $\log_{10}$ 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 MIC_{90} of 0.25 μg/mL versus *C. difficile*, and its main metabolite, OP-1118, has an MIC_{90} 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-ll43-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 observed *in vitro* with rifampicin 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 (µg/mL)**
C. difficile (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 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.

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.

Clinical trials

Clinical Efficacy and Safety

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

Table 3 - 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 4, indicate that DIFICID is superior to vancomycin for this endpoint.

Table 4 - Clinical Response Rates and Sustained Clinical Response Rates (30 Days Post-Therapy)

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

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 5. In both studies, the recurrence rate was significantly lower in the DIFICID group compared to the vancomycin group.

Table 5 - 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).

Efficacy and safety in patients with moderate or severe hepatic impairment, severe renal impairment and fulminant or life-threatening *C.difficile* infection (CDI)

In a retrospective post-authorisation 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). The effectiveness of fidaxomicin treatment, defined as percentage of episodes with resolution of diarrhoea was 83.3% in patients without a medical condition of interest, 78.7% in patients with co-morbid moderate or severe hepatic impairment, 68% in patients with co-morbid severe renal impairment and 67.5% in patients with fulminant or life-threatening CDI. Evaluation of the incidence of mortality, laboratory and ECG data did not indicate any additional safety concern in patients with a medical condition of interest compared with those who did not have any of these conditions.

Efficacy and safety in patients with inflammatory bowel disease (IBD).

In the retrospective post authorisation study 29 CDI patients with co-morbid IBD were included. The effectiveness of fidaxomicin treatment, defined as percentage of episodes with resolution of diarrhoea was 81.8% in CDI patients with IBD and 83.3% in CDI patients without a medical condition. Evaluation of the incidence of mortality, laboratory and ECG data did not indicate any additional safety concern 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. This was associated with similar adverse event reporting as documented in previous studies with CDI patients without IBD. CDI clinical response after fidaxomicin treatment (Day 12) was reported in 20/25 (80%) (95% confidence interval 60.9-91.1%). Of 20 patients with CDI clinical response at Day 12, there were no recurrences at Day 26 and three patients had recurrence by Day 180.

5.2 PHARMACOKINETIC PROPERTIES

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 6 below.

Table 6 - Mean (± Standard Deviation) Pharmacokinetic Parameters of Fidaxomicin and OP-1118 in Healthy Adult Males Following a Single 200 mg Dose

	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng-hr/mL)	AUC_{0-t} (ng-hr/mL)	T_{max} (hr)*	$t_{½}$ (hr)
Fidaxomicin	5.20 ± 2.81 (n=14)	62.9 ± 19.5 (n=9)	48.3 ± 18.4 (n-14)	2.00 (1.00-5.00) (n=14)	11.7 ± 4.80 (n=9)
OP-1118	12.0 ± 6.06 (n=14)	118 ± 43.3 (n=10)	103 ± 39.4 (n=14)	1.02 (1.00-5.00) (n=14)	11.2 ± 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
$AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity
AUC_{0-t}, area under the concentration-time curve from time 0 to the last measured concentration

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 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.

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.

Special populations

Renal Impairment

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

Hepatic Impairment

The impact of hepatic impairment on the pharmacokinetics of fidaxomicin has not been evaluated. Because fidaxomicin and OP-1118 do not appear to undergo significant hepatic metabolism, elimination of fidaxomicin and OP-1118 is not expected to be significantly affected by hepatic impairment. Limited data from patients with an active history of chronic hepatic cirrhosis in the Phase 3 studies showed that median plasms levels of fidaxomicin and OP-1118 may be approximately 2 and 3 fold higher, respectively, than in non-cirrhotic patients.

Geriatric

In controlled trials of patients treated with DIFICID 200 mg twice daily for 10 days, mean and median values of fidaxomicin and OP-1118 plasma concentrations within the T_{max} window (1-5 hours) were approximately 2-4 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.

Race, Gender, and Weight

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

Inflammatory bowel disease

The effect of concomitant inflammatory bowel disease (IBD) on the pharmacokinetics of fidaxomicin and OP-1118 was evaluated in CDI patients. 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 1-5h post dose on the last day of dosing (day 10).

Fidaxomicin and OP-1118 plasma levels in patients with CDI patients with concomitant inflammatory bowel disease (IBD) were within the same range of levels found in CDI patients without IBD 1-5h post-dose on the last day of dosing (day 10).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fidaxomicin 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. Fidaxomicin 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 fidaxomicin is not genotoxic *in vivo* and does not represent a risk of genotoxicity in clinical use.

Carcinogenicity

Carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets:

microcrystalline cellulose

pregelatinised maize starch

hyprolose

butylated hydroxytoluene

sodium starch glycollate

magnesium stearate

Tablet Coating:

polyvinyl alcohol

titanium dioxide

purified talc

Macrogol 3350

lecithin (soy)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

DIFICID tablets are supplied in HDPE Bottles containing 20 and 60 tablets and a desiccant and fitted with a child-resistant cap.

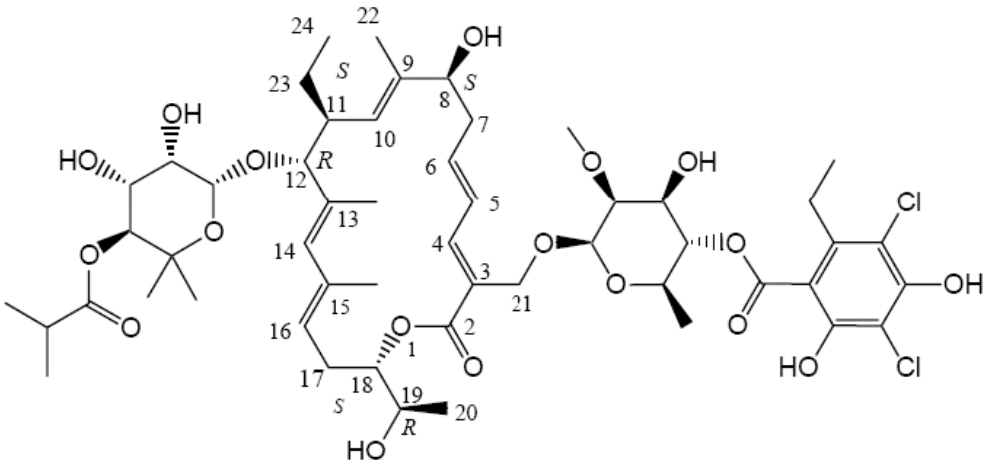
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

873857-62-6

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*,8S,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-.

Molecular weight: 1058.04

Molecular formula: $C_{52}H_{74}Cl_2O_{18}$

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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp and Dohme (Australia) Pty Limited

Level 1, Building A, 26 Talavera Road

Macquarie Park NSW 2113

Australia

9 DATE OF FIRST APPROVAL

23 April 2013

10 DATE OF REVISION

15 June 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Deletion of blister pack presentation from Product Information

RCN: 000022820-AU

CCDS-MK5119-MF-012019