Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fidaxomicin

Proprietary Product Name: Dificid

Sponsor: Specialised Therapeutics Australia Pty Ltd

September 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission	New Chemical Entity
Decision:	Approved
Date of decision:	18 April 2013
Active ingredient:	Fidaxomicin
Product name:	Dificid
Sponsor's name andaAddress:	Specialised Therapeutics Australia Pty Ltd, PO Box 250, East Kew VIC 3102
Dose form:	Tablet
Strength:	200 mg
Containers:	Bottle and Blister pack
Pack sizes:	20's and 60's (bottle) and 20's and 100's (blister pack)
Approved therapeutic use:	Dificid (fidaxomicin) is indicated for the treatment of confirmed *Clostridium difficile* infection (CDI) in adults.
Route of administration:	Oral (PO)
Dosage:	One tablet (200 mg) once every 12 h for 10 days.
ARTG Numbers:	195623 and 195622

Product background

This AusPAR describes the application by the sponsor to register a new chemical entity, Dificid, containing the active ingredient, fidaxomicin. The proposed therapeutic indication is as follows:

> *Dificid (fidaxomicin) is indicated for the treatment of Clostridium difficile infection (CDI), and for reducing the risk of recurrence when used for treatment of 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 diagnosed to be caused by Clostridium difficile.*

The proposed dosing regimen is oral administration of one tablet (200 mg) once every 12 h for 10 days.

Clostridium difficile is a gram-positive, spore-forming, obligate anaerobic bacterium. It is the leading cause of nosocomial diarrhoea in patients undergoing antibiotic treatment and sometimes chemotherapy. *Clostridium difficile* Associated Disease (CDAD) is the result colonisation and production of enterotoxins A and B by this organism in large intestine. The severity of disease can range from mild diarrhoea to fulminant pseudomembranous colitis with complication like toxic megacolon and intestinal perforation. The reported

mortality rates range from 6 to 30%. Community acquired CDAD is also recognised, which case may not be associated with known antibiotic use.

The term *Clostridium difficile* Infection (CDI) is used interchangeably with CDAD. However, CDAD is preferred in this AusPAR as it is unambiguous with respect to intestinal colonisation and disease.

In North America and the European Union (EU), outbreaks of CDAD associated with the emergence of a hypervirulent strain have occurred. The strain is variously known as Toxinotype III, North American Pulsed-field type 1 (NAP1), Restriction Endonuclease Analysis (REA) type BI or Polymerase Chain Reaction ribotype 027 (NAP1/BI/027). This strain has been shown, *in vitro*, to produce 16 to 23 times more toxins A and B than other strains. It also produces a binary toxin.

The current treatment options in management of CDAD include discontinuation of the offending medication, supportive measures and antimicrobials. The two most commonly used antibiotics to treat CDAD are oral vancomycin and metronidazole. Both are associated with a high rate of clinical recurrence. Oral vancomycin is the only antibiotic approved for use in the treatment of CDAD in Australia and acts locally unlike metronidazole which is absorbed well acts systemically after oral administration.

Regulatory status

This product has been approved in the European Union, the USA and Canada for the treatment of *Clostridium difficile* infection (CDI).

Table 1. International regulatory status

Country/Region	Date submitted	If approved	
		Date approved	**Approved indication**
European Union (centralized)*	16 July 2010	5 December 2011	Clostridium difficile infection (CDI)
United States of America	30 November 2010	27 May 2011	Clostridium difficile associated diarrhoea (CDAD)
Canada	2 November 2011	7 June 2012	Clostridium difficile infection (CDI)
Taiwan	13 December 2011	18 July 2012	Clostridium difficile associated diarrhoea (CDAD)
Brazil	20 December 2012	Pending	Clostridium difficile infection (CDI)

Product Information

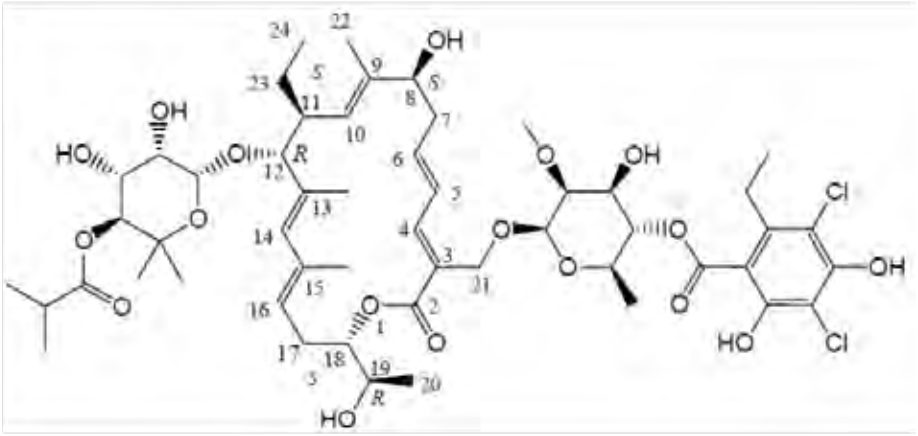
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Fidaxomicin (structure below) is a purified fermentation product produced by the organism, *Dactylosporangium aurantiacum*.

Figure 1. Chemical structure of fidaxomicin



In addition to the chirality associated with the substituted β-D- mannopyranose and β-D-*lyxo*- hexopyranose substituents, the drug substance has five chiral centres but is produced as a single stereoisomer. True polymorphs are not known but fidaxomicin exists in a number of solvated crystalline forms. Fidaxomicin has low solubility and low permeability and absorption and as such, is classified as a BCS[1] Class IV compound. The aqueous solubility is tabulated below; fidaxomicin is chemically unstable outside of the pH range 4-8. It has a pKa of 9.31 (weak acid) and a log P of 3.7 in octanol/water.

Table 2. Aqueous solubility

pH	Solubility (µg/mL)		
	1 hour	2 hours	24 hours
4	< 0.06	< 0.06	NA
6	< 0.06	< 0.06	NA
7	18.35	18.67	16.81
8	103.71	97.92	76.42

A three-tier particle size limit has been proposed, given the demonstrated poor solubility of the drug substance over the pH range of 4-8.

There are a large number of impurities in the drug substance that are controlled at levels above the relevant International Conference on Harmonization (ICH) qualification threshold. Some have been adequately qualified, but the Medicines Toxicology Evaluation Section at the TGA has advised that the limits for several impurities have not been toxicologically qualified.

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Drug product

The drug product, an immediate release tablet containing fidaxomicin 200 mg, is a white to off-white, film-coated, capsule-shaped tablet debossed with "FDX" on one side and "200" on the other side. Two packaging configurations are proposed:

- white High Density Polyethylene (HDPE) bottles with tamper-evident, induction sealed, polypropylene child-resistant caps, and containing a silica/activated carbon desiccant.
- polyamide/aluminium foil/polyvinyl chloride (PVC)/aluminium foil blisters.

The excipients include the antioxidant butylated hydroxytoluene.

The choice of dissolution medium was limited due to the chemical instability of fidaxomicin outside the pH range 4 - 8, and the virtual insolubility of the drug substance in this range.

The stability data support a shelf life of 36 months stored below 25°C in both proposed packaging types.

As with the drug substance, the Medicines Toxicology Evaluation Section has advised that the limits proposed for the seven identified and three unidentified impurities controlled in the finished product specifications have not been toxicologically qualified.

Biopharmaceutics

Study OPT-80-005 determined the pharmacokinetics of fidaxomicin, and assessed the effects of a high fat meal on drug bioavailability relative to the fasted state following administration of 2 x 200 mg of the proposed commercial formulation. The active metabolite, OP-1118, was also monitored. The following outcomes were obtained:

Table 3. Fidaxomicin: treatment B versus A (fed versus fasting)

	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng.h/mL)
A: fasting	1.00	8.94	73.0
B: fed	2.00	7.02	70.6
Statistical analysis:	***median diff***	***ratio (%)***	***ratio (%)***
B *versus* A estimate	-	78.5	96.7
90% confidence interval	-	(67.26 – 91.69)	(87.04 – 107.43)

Table 4. Fidaxomicin metabolite, OP-1118: treatment B versus A (fed versus fasting)

	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng.h/mL)
A: fasting	1.00	22.4	162
B: fed	2.00	14.9	146
Statistical analysis:	***median diff***	***ratio (%)***	***ratio (%)***
B *versus* A estimate	-	66.6	89.7
90% confidence interval	-	(58.37 – 75.97)	(82.46 – 97.65)

Thus, for fidaxomicin and its metabolite, the extent of exposure (area under the plasma concentration time curve over a dosing interval; AUC0-t) but not the peak plasma exposure (Cmax), was equivalent in the fed state compared to the fasted state. Consumption of a high-fat meal led to a slightly delayed time to peak plasma concentration (Tmax)of 1 h and a 22% and 33% reduction in Cmax, with respect to fidaxomicin and its metabolite, OP-1118. The applicant has stated that these 'small' differences in C_{max} are not considered to have clinical relevance, given that systemic exposure is not relevant to efficacy for *Clostridium difficile* infections, which are confined to the gut. No mention of these results is made in the draft Product Information leaflet. This has been drawn to the attention of the Delegate.

A justification for not providing an absolute bioavailability study was provided. The justification has been accepted by the evaluator and the Delegate.

Advisory committee considerations

This submission was reviewed at the 148th meeting of the Pharmaceutical Sub Committee (PSC) of the Advisory Committee on Prescription Medicines.

The following recommendations (Recommendation No 2289) were given:

1. The PSC endorsed all the issues raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the application submitted by Novotech Australia Pty Ltd to register Dificid film coated tablet containing 200 mg of fidaxomicin. The sponsorship of this product has since been transferred to Specialised Therapeutics Australia Pty Ltd.
2. The PSC supported the questions on the limits for impurities in the drug substance and degradants in the drug product specifications.
3. The PSC advised that the sponsor should be asked to:
   - Provide batch analysis and stability data generated using drug substance manufactured at the two nominated drug substance manufacturing sites.
   - Ensure that the drug substances from the two nominated manufacturing sites are represented in the batch analysis and stability trials for the drug product.
4. The PSC agreed that the attention of the Delegate and the Advisory Committee on Prescription Medicines (ACPM) should be drawn to the lower availability of fidaxomicin metabolite from the formulation when administered under fed conditions as this may have clinical implications.
5. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the ACPM

Quality summary and conclusions

The company has provided satisfactory responses to the questions that were raised following the initial evaluation of this submission. There were no objections in respect of Chemistry, Manufacturing and Controls to registration of fidaxomicin ("Dificid") 200 mg tablets with a shelf life of 3 years below 25°C.

However, it should be noted that the Medicines Toxicology Evaluation Section at the TGA has advised that the limits proposed for ten impurities in the drug substance and finished product specifications have not been adequately toxicologically qualified.

The Provisional Australian Register for Therapeutic Goods (ARTG) Records were considered accurate.

The revised PI submitted with the consolidated response is satisfactory with respect to chemical and pharmaceutical matters.

The Delegate should note the following:

1. The current [at the time of the quality evaluation report] Good Manufacturing Practice (GMP) clearance for the principal manufacturer expired on 31 December 2012.
2. Ten impurities in the drug substance and finished product specifications have not been adequately toxicologically qualified.
3. In the first round evaluation of the chemistry and quality control data, the evaluator sought clinical comment on:
   - the company's justification for not performing an absolute bioavailability study;
   - the significance of the reduction in Cmax when fidaxomicin tablets are taken with food.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical studies was high. A number of approaches were taken in an attempt to increase systemic exposure for animal toxicity studies. Furthermore, analytical methods were developed to allow detection of very low fidaxomicin levels in plasma and faeces (low nanomolar range) which has contributed greatly to the quality of the nonclinical studies. Pivotal studies examining repeat dose toxicity, reproductive toxicity, genotoxicity and safety pharmacology were conducted under Good Laboratory Practice (GLP) conditions. No carcinogenicity studies were submitted which was considered acceptable due to the overall negative genotoxicity results, the low systemic exposure and the proposed short treatment duration.

Pharmacology

Fidaxomicin is the first member of a new class of antibiotics termed macrocycles and is derived from fermentation of *Dactylosporangium aurantiacum* subspecies hamdenensis.

Primary pharmacology

Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacterium. Disruption of the normal gastrointestinal flora, for instance due to antibiotic therapy, can be followed by overgrowth with toxin producing *Clostridium difficile* strains inducing potentially fatal diarrhoea. Fidaxomicin is intended for treatment of this gastrointestinal infection.

Desirable drug qualities are therefore a narrow antibiotic spectrum, mainly targeting *Clostridium difficile*, and low absorption from the gastrointestinal tract to maximise exposure at the intended site of action.

Mechanism of Action

Fidaxomicin is proposed as an antibacterial agent. Fidaxomicin (also known as Tiacumicin B), has moderate activity against most Gram-positive bacteria and is bactericidal against *Clostridium difficile*. The mechanism of action is proposed to be inhibition of transcriptional initiation, by inhibition of ribonucleic acid (RNA) polymerase, possibly by a unique mechanism, although this was not investigated in detail.

Fidaxomicin and its main metabolite (OP-1118) also inhibited production of *Clostridium difficile* spores *in vitro* without affecting the titre of pre-existing spores at sub minimum inhibitory concentrations (MICs).[2]

Antibacterial activity

Results from the literature, including a study that investigated 110 molecularly distinct isolates and two Phase III trials that included 800 clinical isolates investigated the antibacterial efficacy against different strains of *Clostridium difficile*. Typical MIC_{90} values were similar against these different *C. difficile* types and ranged from 0.125-0.25 μg/mL. Even though different strains showed different susceptibilities, all MIC90 values were below 1 μg/mL. In the presence of faecal material, MIC values of fidaxomicin against *Clostridium difficile* increased to 2 μg/mL. Over a 48 h period the bactericidal activity of fidaxomicin was time dependent and not concentration dependent above the MIC.

Fidaxomicin was moderately selective for *Clostridium difficile* when tested against 10 other *Clostridium* strains. For the responding half of the strains (*bifermentans, glycolicum, paraputrificum, perfringens* and *sordellii)* MIC values ranged from 0.06-1 μg/mL, whereas in the less sensitive strains, MIC values ranged from 1-512 μg/mL.

Antibacterial activity against bacteria other than *Clostridium* strains was investigated in two studies as well as 4 published studies.[3, 4, 5, 6] A summary of tested strains and IC_{50} and IC_{90} values was given in the submission. Fidaxomicin was shown to have a narrow antibiotic spectrum with poor activity against Gram negative bacteria (MIC required to inhibit the growth of 50% and 90% of organisms (MIC_{50} and MIC_{90} respectively) values >100 μg/mL). Fidaxomicin was more effective against Gram positive anaerobic bacteria but showed pronounced variation between genera (MIC_{90} range from 0.016-32 μg/mL). Fidaxomicin also showed some activity against Gram positive aerobic/faculatative bacteria (*Streptococcus, Enterococcus, Staphylococcus aureus and epidermidis)* with MIC_{90} values ranging from 2-32 μg/mL. Fidaxomicin had no activity against yeast.

Antibacterial activity of the main fidaxomicin metabolite OP-1118 was investigated *in vitro*. The metabolite's antibiotic spectrum was also narrow in range with generally lower

[2] Babakhani L et al. Fidaxomicin Inhibits Spore Production in Clostridium difficile. Manuscript Submitted to Clinical Infection Diseases, 2011

[3]Ackermann G et al. (2004). In Vitro Activity of OPT-80 against Clostridium difficile. Antimicrobial Agents and Chemotherapy, 48(6):2280-2282

[4]Finegold SM et al (2004). In Vitro Activities of OPT-80 and Comparator Drugs against Intestinal Bacteria. Antimicrobial Agents and Chemotherapy 48(12):4898–4902

[5]Credito KL et al (2004). Activity of OPT-80, a Novel Macrocycle, Compared with Those of Eight Other Agents against Selected Anaerobic Species. Antimicrobial Agents and Chemotherapy 48(11) p. 4430–4434

[6]Hecht DW et al (2007). In Vitro Activities of 15 Antimicrobial Agents against 110 Toxigenic Clostridium difficile Clinical Isolates Collected from 1983 to 2004. Antimicrobial Agents and Chemotherapy 51 (8) p. 2716–2719

activity than the parent fidaxomicin. The MIC_{90} against *Clostridium difficile* was 8 µg/mL. MIC values were reported to increase in the presences of faeces, likely due to faecal binding of the metabolite but MIC values were still substantially below concentrations of ~1 mg/g reported in the faeces. The activity of the metabolite OP-1118 against other anaerobic flora was >16 µg/mL (with the exception of *Bifidobacterium longum* (MIC 1 µg/mL), *Finegoldia magna* (MIC 8 µg/mL), *Peptoniphilus asaccharolyticus* (MIC 4 µg/mL), *Peptostreptococcus anaerobius* (MIC 0.25 µg/mL) and *Micromonas micros* (MIC 1 µg/mL). After oral administration of fidaxomicin, OP-1118 is found in high concentrations (~1 mg/g) in the gastrointestinal tract. It is considered likely to contribute to the overall antibiotic effect.

The *in vitro* studies indicating a narrow antibiotic range with specificity towards *C. difficile* supports the proposed indication for the treatment of *C. difficile* infection and would allow for repopulation of the physiological gastrointestinal flora.

The efficacy of fidaxomicin against 3 different *Clostridium difficile strains (4325-M01, TTU 614, ATCC43255-A01)* was confirmed *in vivo* using an established hamster model of clostridium infection. Before inoculating animals with *C. difficile* vegetative cells or spores, animals were pre-treated with a broad spectrum antibiotic to destroy the physiological gastrointestinal flora in order to promote overgrowth with pathogenic *C. difficile*. Fidaxomicin was shown to be effective in preventing *Clostridium difficile* induced lethal infection with the amount o required to produce a specific effect in half of an animal population being ED_{50} < 0.3 mg/kg in the hamster. This is well below the proposed clinical dose of 4 mg/kg, calculated for a 50 kg patient. Technical issues made the results of two of the studies difficult to interpret. The vehicle unexpectedly rendered the treatment ineffective in one study, although this result was not repeatable in a follow up study. In a different study, uncontrolled infection with a wild *Clostridium difficile* strain caused high mortality in the control group. Based on survival during the 7 day treatment period fidaxomicin treatment was as effective as vancomycin but more effective than metronidazole. However, large numbers of animals in the fidaxomicin and metronidazole groups redeveloped infection after removal of treatment, and 30 day survival was low, whereas the vancomycin group exhibited superior 30 day survival. The reason for differences in recurrence is not known. *C. difficile* isolates from the faeces of all groups showed similar MIC values for fidaxomicin.

Antibiotic interaction

The interaction of fidaxomicin and its main metabolite OP-1118 with members of other antibiotic classes (ampicillin, azithromycin, ciprofloxacin, clindamycin, metronidazole, rifampin, rifaximin, telithromycin and vancomycin) was investigated against *C. difficile*. No antagonistic interaction was observed with fidaxomicin or the metabolite OP-1118. Both rifamycins, rifampin and rifaximin, which also act as polymerase inhibitors, as well as ampicillin, a cell wall synthesis inhibitor, and metronidazole, which inhibits nucleic acid synthesis by disrupting DNA, were synergistic with fidaxomicin and OP-1118. Fidaxomicin, but not the metabolite, showed synergy with clindamycin (a translation inhibitor targeting the 50S ribosomal subunit).

Post-antibiotic effect

A post-antibiotic effect, of 5.5 – 10 h was reported for fidaxomicin when tested against a clinical isolate (LC3) and a laboratory strain (ATCC 43255) of *Clostridium difficile* in cell culture. The post-antibiotic effect was measured as the delay in bacterial regrowth after termination of a 1 h treatment period (4 × MIC) by removal of the antibiotic through washing and centrifugation. Delay was calculated as the length of time required for the post-wash titre to increase one log, minus the time required for the control to increase one

log. The major metabolite, OP-1118, also had a post-antibiotic effect, though shorter than that of the parent compound.

Resistance

The frequency of spontaneous resistance development was measured in different *C. difficile* strains (ATCC 9689, 17857, 43255 and 700057 plus two clinical strains ORG911 and 916) in the presence of 4 or 8× the MIC. The frequency of spontaneous resistance development was very low but similar to vancomycin and metronidazole. Only a few resistant isolates were observed with fidaxomicin at 4× MIC in some of the ATCC strains. All 4 of the tested isolates produced resistance to rifamycin at 8 x MIC. A low propensity to develop spontaneous resistance to fidaxomicin was also observed by serially passaging *C. difficile* ATCC 43255 in the presence of fidaxomicin. The low frequency of spontaneous resistance *in vitro* is an indication that resistance development *in vivo* is likely to be slow.

Modification of the fidaxomicin target, RNA polymerase, was investigated as a possible mechanism of resistance. Ten fidaxomicin-resistant clones were generated by either nitrosoguanidine treatment or by spontaneous means, after plating wild type strains at 4× MIC. The genes comprising the RNA polymerase core enzyme (*rpoA*, *rpoB*, and *rpoC*) of fidaxomicin resistant *C. difficile* clones were sequenced and analysed for mutations. Sequencing focused primarily on the β and β' subunits, since these had previously been identified as resistance sites for the related compound lipiarmycin.[7, 8] Sequencing of the fidaxomicin resistant clones showed mutations of four residues in *rpoB* and two residues in *rpoC*. A summary table of amino acid mutations that confer reduced fidaxomicin sensitivity was included in the submission. In the Phase III clinical studies (101.1.C.003 and 101.1.C.004), most isolates had a similar MIC (<1 μg/mL) at the beginning and end of the 10 day treatment period. Additional isolates were collected in cases of early termination, or recurrence over a 28 day follow up period. With the exception of one subject where isolates collected at baseline and the end of the treatment period had MIC values of 0.06 μg/mL, but the *Clostridium* strain isolated at recurrence of infection in this subject had an MIC value of 16 μg/mL and was shown to have a mutation for *rpoB*, which encodes the β-subunit of RNA polymerase. Mutations in the fidaxomicin target RNA polymerase therefore appears to reduce the susceptibility of *Clostridium difficile* to fidaxomicin.

Cross resistance of fidaxomicin was tested by evaluating the susceptibility of a *C. difficile* strain with reduced fidaxomicin sensitivity against other antibiotics. The mutant did not show reduced susceptibility towards azithromycin, telithromycin, ampicillin, aztreonam, cefotaxime, ciprofloxacin, vancomycin, metronidazole, rifampin. In the reverse experiment, organisms resistant to other antibiotics were tested for reduced susceptibility towards fidaxomicin. No cross resistance of fidaxomicin with antibiotics targeting mechanisms other than deoxyribonucleic acid (DNA) replication or transcription, including macrolides, β–lactams and vancomycin was detected. Furthermore, no cross resistance with other RNA Polymerase inhibitors (rifampin) or DNA synthesis inhibitors (fluoroquinolones or metronidazole) was detected suggesting a unique mechanism of action. The sponsor's risk assessment of antibiotic resistance development was also included in the submission.

[7]Gualtieri M et al (2006). Mutation in the Bacillus subtilis RNA Polymerase Subunit Confers Resistance to Lipiarmycin. Antimicrobial Agents and Chemotherapy 50 (1) p. 401–402
[8]Kurabachew M et al (2008). Lipiarmycin targets RNA polymerase and has good activity against multidrug-resistant strains of Mycobacterium tuberculosis. Journal of Antimicrobial Chemotherapy 62: 713–719

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamics of fidaxomicin were not reported. Due to the anticipated low systemic exposure to fidaxomicin, and adequate safety pharmacological and repeat dose toxicological testing that showed low systemic or local toxicity, the absence of *in vitro* screening assays for ligand binding or enzyme activity to investigate the off target mode of action or effects of fidaxomicin is considered acceptable.

Specialised safety pharmacology studies were conducted with fidaxomicin and covered the core battery of systems; central nervous system (CNS; rat), cardiovascular (dog) and respiratory (rat). The main metabolite OP-1118 is rapidly generated *in vivo* and was thus not assessed separately, except for the *in vitro* study.

No treatment related CNS or respiratory effects were observed with fidaxomicin or its main metabolite OP-1118 in rats. CNS toxicity was investigated through functional assessment after intravenous (IV) fidaxomicin in 1% Solutol at doses of up to 7.5 mg/kg in male rats, associated with fidaxomicin plasma levels of up to 2470 ng/mL (OP-1118 up to 2160 ng/mL) 15 min post injection, up to 249 fold (OP-1118: 123 fold) the clinically anticipated C_{max} exposure. Respiratory function was unaffected after IV administration of up to 7.5 mg/kg fidaxomicin in 1% Solutol to male rats, associated with plasma concentrations of up to 30500 ng/mL 15 min post injection (OP-1118 up to 5250 ng/mL), 3081 fold (OP-1118: 298 fold) the clinical plasma C_{max} of 9.9 ng/mL fidaxomicin and of 17.6 ng/mL OP-1118, reported after a single 200 mg dose. After IV administration of 1 mg/kg fidaxomicin in 1% Solutol to beagle dogs 'histamine – like' clinical signs were observed including redness of eye and skin, prostration, salivation, defecation, breathing difficulty and decreases in systolic and diastolic blood pressure without other changes on electrocardiogram (ECG) parameters. These symptoms were associated with a mild seizure in one female dog. No other cardiovascular findings were observed. The solubiliser Solutol has previously been associated with elevated histamine plasma levels.[9]. It is possible that Solutol induced these effects in dogs since histamine like effects or treatment related cardiovascular effects were not observed in the absence of Solutol in another study. In this study, fidaxomicin was administered orally (PO) to dogs in gelatine capsules (~1129 mg/kg), associated with fidaxomicin plasma levels of up to 4190 ng/mL, 423 fold the clinically proposed concentration (OP-1118: 441ng/mL, 25 fold the clinically proposed concentration). These plasma levels exceeded the concentrations that induced histamine like effects in the presence of Solutol in the dog IV study.

Neither fidaxomicin nor the main metabolite OP-1118 induced inhibition of the potassium (hERG channel) current at concentrations up to 7.85 and 8.37 µg/mL, respectively.

Given the high safety margin, no adverse effects on CNS, cardiovascular or respiratory function is predicted to occur clinically.

Pharmacokinetics

Absorption: Fidaxomicin and its main metabolite OP-1118 (desisobutyryl fidaxomicin) are Class IV compounds, possessing low solubility and permeability. Additionally, fidaxomicin was actively effluxed by P-glycoprotein in an *in vitro* model of the gastrointestinal barrier, which would further limit gastrointestinal absorption (see pharmacokinetic drug interaction below). In an effort to increase oral bioavailability or solubility in solutions for IV administration to maximise systemic exposure, the sponsor tested a range of different solubilising agents (Solutol, Labrasol) and self emulsifying systems, (LT-1, LT-2, MT-1, MT-2). Several of these drug delivery systems were not well tolerated in dogs (LT-2, Solutol).

[9] Ruchatz F, Applications of Solutol® HS 15 – A potent solubilizer with a low toxicity. BASF ExAct No 9 October 2002

Exposure was variable after IV and highly variable after PO administration to rats and dogs. In humans, particularly in *Clostridium difficile* infected patients exposure was also highly variable after oral administration. No consistent sex differences were observed in all species including humans. Absorption after oral administration was rapid, but low, in humans and dogs with highest plasma levels reached after 1-1.5 h in dogs and humans. Most of the drug related material remained in the gastrointestinal tract, the intended site of action. Intravenous studies could not be conducted in humans due to the low aqueous solubility of fidaxomicin preventing solubilisation in an IV formulation acceptable for human use. Despite efforts to increase solubility and permeability of fidaxomicin in animal studies, absorption from the gastrointestinal tract was also very low. Bioavailability measured in dogs was <3% in the presence of self emulsifying drug delivery systems. Exposure following intravenous administration was limited by solubility and the maximum feasible dose volume for the species. Nevertheless, in animal studies, high systemic exposure in the range of 1-33 µg/mL was achieved by administration of high doses to rats (IV, up to 2 mg/kg) and dogs (PO, up to 120 mg/kg; IV up to 4 mg/kg). C_{max} and AUC appeared to increase greater than dose proportional after PO administration of nominal doses of 10-120 mg/kg, though these results are compromised by the high variability of the data set. There was no evidence of systemic accumulation with repeated oral dosing of fidaxomicin in rats, dogs, monkeys or humans though again, the high variability of the dataset introduces uncertainty to this finding. The half-life ($t_{1/2}$) of fidaxomicin after IV administration of 1-7.5 mg/kg was ≤ 1h in rats and dogs and increased with increasing dose in both species. Similarly, clearance decreased with increasing dose (rats: 72-31; dogs 28-3 mL/min/kg). The volume of distribution was similar in rats and dogs (107-616 mL/kg) and generally less than total body water indicating circulating plasma concentrations are a good measure of the systemic fidaxomicin exposure.

The main human metabolite OP-1118 was also rapidly formed in rats after single IV administration and dogs after single PO administration (T_{max} ≤ 2 h), though to a lesser extent than in humans. The AUC exposure ratio of OP-1118 to fidaxomicin was 0.2-0.3 in rats and dogs compared to healthy humans where metabolite levels were observed to be 2 fold greater than the parent (2 to 6 fold in CDI patients). The plasma kinetic profile for the metabolite OP-1118 generally mirrored the parent. Determination of OP-1118 half life was compromised by low metabolite levels which made the slope calculation unreliable in dogs (range $t_{½}$ 0.9 to 49 h) and short in rats ≤ 0.37h. Biotransformation of fidaxomicin to OP-1118 saturated with higher doses in dogs after IV but not PO dosing.

Distribution: Protein binding was high for fidaxomicin in all species (96-99%) in the order rabbit > human > dog > rat. For the main metabolite, OP-1118, protein binding ranged from 91-98% with the order rabbit > human > rat > dog. As a drug that is highly bound to protein, fidaxomicin would be expected to remain mainly in the blood compartment. In support of little distribution from blood into tissue, the total volume of distribution for fidaxomicin was reported to be less than body water.

Fidaxomicin is minimally absorbed after oral administration in all species, with most of the fidaxomicin remaining in the faeces. In dogs >99% of the radioactivity remained in the faeces (measured over 168 h, 87% total recovery). The gastrointestinal (GI) tract is therefore the main site of exposure. After a nominal dose of ~ 460 mg/kg, mean faecal concentrations of fidaxomicin were 4760-13,600 µg/g. The only distribution study that was conducted investigated the PO route and failed to achieve sufficiently high systemic exposure to allow detection of radioactivity in tissues or body fluids, or analytical determination of fidaxomicin in plasma. Fidaxomicin and its main metabolite are substrates for P-glycoprotein; this could also contribute to the low absorption of the compound.

Metabolism: The main metabolite of fidaxomicin is the hydrolysis product OP-1118, or desisobutyryl fidaxomicin. It was found in rats, dogs, monkeys and humans and has antibacterial pharmacological activity. Faecal recovery after a single oral dose showed that metabolism to OP-1118 was most extensive in humans (26% excreted as unchanged drug whereas 66% was excreted as OP-1118. However human faecal fidaxomicin concentrations were higher than OP-1118 concentrations after repeat dosing for 10 days. All other metabolites were minor. Acyl migration, to form the tiacumicins C and/or F, was observed in the plasma from dogs and humans. The $AUC_{0\text{-last}}$ ratios of tiacumicins C and F were 1.4 and 5% of the parent fidaxomicin in dogs dosed PO. Similarly, in human plasma Tiacumicin F accounts for less than 3% of the total absorbed parent compound, whereas Tiacumicin C was not detected. Monohydroxylation of fidaxomicin and the main metabolite OP-1118 was also observed in human and dog liver microsomes and hepatocytes. Trace amounts of two conjugates were also detected, a sulfate conjugate formed by dog and human liver hepatocytes and a glucuronide conjugate detected in dog hepatocytes only. The hydroxylation products and conjugates were not observed in dog or human urine, plasma, or faeces, but sulfation and glucuronidation products have been observed in dog bile. No human specific metabolites were found.

Gastrointestinal metabolism of fidaxomicin was shown to occur in rats, dogs, monkeys and humans. Gastrointestinal metabolism of fidaxomicin appears to be particularly rapid in rats, with a half life of 10 min compared to > 60 min in dogs, cynomolgus monkeys and humans, making the rat unsuitable as a model for oral studies. In dogs, presystemic hydrolysis of fidaxomicin to OP-1118 specifically was shown by high levels of the main metabolite in the faeces (69-251 µg/g after a 461 mg/kg nominal dose, PO). Formation of OP-1118 was shown to be independent of nicotinamide adenine dinucleotide (NADPH) and likely catalysed by an esterase. Hydrolysis to OP-1118 and acyl migration to the tiacumicins C and F can also occur non-enzymatically in aqueous solutions at physiological temperature and pH.

The metabolism of fidaxomicin was shown to be largely independent of cytochrome P450 enzymes. The only cytochrome P450 (CYP) isoform that was shown to be marginally involved in the generation of OP-1118 was CYP3A4. CYP2C9 possibly contributes to metabolism of an unidentified, but minor fidaxomicin metabolite. This is not thought to be of clinical relevance.

Excretion: Drug related material, almost exclusively fidaxomicin and OP-1118, was excreted almost completely via the faecal route following oral administration, >90% in dogs and humans. In dog faeces only 1.3% was recovered as OP-1118. Urinary excretion was negligible constituting <1% of administered dose in dogs and humans. Biliary excretion was demonstrated in dogs but the overall contribution to excretion was very minor; less than 1% of the administered dose. The high faecal levels of drug related material is attributed to poor gastrointestinal absorption.

Conclusion: The pharmacokinetic profile in dogs was thought to be adequately similar to humans in terms of absorption, distribution, metabolism and excretion for this species to serve as a good animal model for the toxicity studies. Pharmacokinetics in rats appears to be more different to humans especially in terms of gastrointestinal metabolism.

Pharmacokinetic drug interactions

P-glycoprotein: Fidaxomicin and its main metabolite, OP-1118, are substrates for the efflux pump, P-glycoprotein. However, given the low solubility and permeability of fidaxomicin, P-glycoprotein inhibitors are unlikely to significantly affect the systemic exposure to fidaxomicin. Fidaxomicin was also shown to inhibit P-glycoprotein with an IC_{50} of 2.59 µM (2.7 µg/mL). The metabolite OP-1118 showed 43.1% inhibition at 125 µM (124 µg/mL). Sufficiently high concentrations to inhibit P-glycoprotein systemically are not expected

with the proposed dosing. The possibility of inhibition of gastrointestinal P-glycoprotein cannot be excluded, given the high intestinal concentration (800 µg/mL, 200 mg single dose in 250 mL).

CYP450 inhibition: In vitro studies in human liver microsomes showed that fidaxomicin inhibited CYP2C9 with an IC50 of 7.2 µg/mL. At 10 µg/mL fidaxomicin showed low inhibitory activity (9-43%) against all other tested enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. The main fidaxomicin metabolite (isobutyryl fidaxomicin) directly inhibited CYP3A4/5 (IC50 values of 42 - 620 µg/mL). Considering the low clinical systemic exposure (0.0106 µg/mL) systemic interaction with the cytochrome P450 system is highly unlikely. However, CYP enzymes are also present in the intestinal mucosa. Since the major site of action (and distribution) of fidaxomicin is the gastrointestinal tract, where much higher concentrations are reached, an effect on intestinal CYP enzymes such as CYP3A or CYP2C9 cannot be excluded.

CYP450 induction: Neither fidaxomicin nor the main metabolite induced major CYP enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5).

In summary fidaxomicin could potentially alter the systemic exposure of orally administered drugs that are substrates of P-glycoprotein or CYP3A or CYP2C. P-glycoprotein inhibitors and CYP450 inhibitors are likely to have minimal impact on the systemic and local exposure of fidaxomicin.

Toxicology

Acute toxicity

Single dose toxicity studies were performed using rats given PO doses up to 1000 mg/kg and IV doses up to 200 mg/kg and dogs given PO doses up to 120 mg/kg and IV doses up to 7.5 mg/kg. A range of different vehicles were used in these experiments (Labrasol, 10% dimethyl acetamide/20%ethanol/70%PEG400, LT-2, 1% solutol HS15 PBS).

The conduct of the set of rodent studies was mostly in accordance with the European Union (EU) Note for guidance on single-dose toxicity (3BS1a)[10]; more than one mammalian species was used, animals of both sexes were examined, the clinical (PO) and IV routes were used. Only two of the rat studies were designed to incorporate a 14 days observation as recommended by the guideline. Furthermore not all animals were subjected to necropsy, which was only conducted in 2 rat studies but not in dogs.

IV injection of doses of 100 and 226 mg/kg fidaxomicin to rats induced 50% mortality. Possible cause of death was the precipitation of fidaxomicin in the vasculature due to its low solubility in aqueous media (0.01 to 0.02 mg/mL). In these studies fidaxomicin was injected at concentrations in excess of solubility (100 or 200 mg/mL solution). No other mortality was observed in any single dose study. IV administration in rats was associated with decreased activity, slightly uncoordinated gait, limited use of hindlegs and opening and closing of mouth from 75 mg/kg and with severe decrease in activity , laboured respiration, gasping and muscle twitches from 100 mg/kg. Oral doses of up to 1000 mg/kg in rats induced only minor clinical signs, including bright yellow urine, few faeces, anogenital staining. Gross pathology revealed no treatment related effects. In dogs PO treatment with nominal doses up to 120 mg/kg induced no mortality and only minor clinical signs (abnormal excreta, excessive salivation and emesis). IV doses up to 7.5 mg/kg (nominal) in dogs induced more marked clinical signs such as swelling, difficult breathing, salivation, tremors, lacrimation, stereotypy and decreased activity, although this could be associated with the vehicle.

[10] <http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf>

The maximum non lethal IV dose in rats was 70.7 mg/kg, this actual dose was associated with plasma levels of 3000 to 10200 ng/mL 30 min after dosing, at least 300-fold the clinically expected exposure. The maximum non lethal dose (nominal) for PO administration in rats was >1000 mg/kg.

Over all the acute toxicity of fidaxomicin after PO dosing is considered to be very low.

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 1 month duration were conducted in rats, 3 months in dogs and 1 month in monkeys. All pivotal studies were conducted by the clinically intended oral route. Additional IV studies for up to 14 days were conducted in rats. All studies implemented a once daily dosing regimen instead of the twice daily administration proposed clinically. This was considered acceptable in the pivotal oral dog and monkey study due to the adequate systemic concentrations achieved with once daily dosing over the 24 h period, especially after administration of the high dose. Fidaxomicin was below detection level after once daily dosing in the pivotal rat study. A number of vehicles were used by the sponsor in an attempt to increase systemic exposure to fidaxomicin. Some of the vehicles led to severe toxicity after repeat dosing, including the vehicle LT2 that had achieved the highest bioavailability of fidaxomicin but induced anaphylactoid reactions in dogs. An IV vehicle used successfully in the single dose toxicity studies in rats (10 % dimethyl acetamide, 20 % ethanol (EtOH), 70 % PEG 400) was lethal in the repeat dose setting. The vehicle used in the pivotal rat and monkeys studies was Labrasol. In the pivotal dog study fidaxomicin tablets (the intended clinical formulation) were administered inside gelatin capsules. The large amount of tablets that were administered in the dog study induced emesis. Toxicity studies largely conformed to TGA adopted EU guidelines[11] in terms of exposure to the main human metabolite, species used (rats, dogs and monkeys), group sizes and the use of both sexes. The duration of the studies was acceptable due to the short duration of the intended clinical treatment (10 days). The highest oral doses were clearly the maximum doses feasible (Table 9).

Relative exposure

Exposure ratios have been calculated for fidaxomicin and its main metabolite as animal: human ratios based on plasma $AUC_{0\text{-last}}$ (animals) and $AUC_{0\text{-}24h}$ (humans) or C_{max} for systemic exposure and, for local exposure in the gastrointestinal tract, as faecal animal: human concentrations on a µg/g basis (Tables 8 and 9). The systemic exposure ratios were calculated using data from healthy subjects. Pharmacokinetics were also conducted in patients with *Clostridium difficile* infection but were not used here since many values were below detection level. If measurable, plasma concentrations in patients were highly variable and generally 2 to 6 fold higher than in healthy individuals but still in the low ng/mL range. While the exposure ratios reported here might be overestimates, there is sufficient margin to accommodate the variability in systemic exposure in patients. Therefore, this is not thought to impact on the safety assessment.

Exposures were combined for males and females since no sex differences were observed. AUC animal to human systemic fidaxomicin exposure ratios were very high in the repeat dose dog studies and adequate in the monkey study. Fidaxomicin concentrations were lower than the limit of quantification (0.5 µg/mL) in the rat oral repeat dose study, probably due to rapid metabolism of fidaxomicin in the gastrointestinal tract. Systemic exposure to the main metabolite was investigated in repeat dose dog studies only and was adequate (Table 6). One dog study additionally investigated plasma levels of the acyl-

[11] CPMP/SWP/1042/99 Rev1 Guideline on repeated dose toxicity. <http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf>

migration products Tiacumicin C and F. Exposure to Tiacumicins was similarly low in dogs and humans (AUC ratio 1-3, Table 7).

The local exposure ratios that were observed in the gastrointestinal tract were adequate and high (16 to167 fold) after administration of the high dose in the pivotal dog repeat dose toxicity study (Table 8). Local exposure to the main metabolite OP-1118 observed in the animal studies was generally lower than in humans (ratio 0.2 to 1.6 fold). Due to the lower activity of the fidaxomicin metabolite compared to the parent, this is not regarded as a safety concern.

Several studies are excluded from this assessment since they were confounded either due to severe toxicity of the vehicle (rat IV study, dog PO study), severe inflammation induced by implantation of permanent placed catheters (rat IV study) or insufficient dosing due to accidental removal of fidaxomicin from the injection solution (0.03 animal:human dose ratio[12]) (rat IV).

Table 5. Relative exposure to fidaxomicin at the end of repeat-dose toxicity studies

Species	Study duration (number)	Route	Dose (mg/kg/day) *Actual or Nominal*	AUC_{last} (µg.h/mL)	Exposure ratio# *AUC*
Dog beagle	14 days WIL-609005	PO Capsule	58 *N*	0.09	1
			144 *N*	0.3	4
			461 *N*	2	24
	14 days WIL-609007	PO Capsule	771 *N*	4.7	58
			1067 *N*	16	196
	14 days WIL-609002	PO gavage	30 *N*	2.4 – 7.6	29-93
			60 *N*	1.7 – 8.5	21-104
			120 *N*	6	73
	3 month WIL-609006	PO Gavage	108 *N*	0.7	9
			364 *N*	5.4	66
			1038 *N*	11.2	137
Monkey Cynomolgus	4 weeks 2002-4923	PO capsule	34 *A*	0.25	3
			102 *A*	0.75	9
Human healthy volunteers	Single dose	PO	[400 mg]	0.0817	

= animal:human plasma AUC0–24 h ; ND-not detected in plasma, LLOQ=0.5 µg/mL

[12] Human dose in mg/m2 calculated for a 50 kg person using the conversion factor 33

Table 6. Relative exposure to the fidaxomicin metabolite OP-1118 in repeat-dose toxicity studies

Species	Study duration (number)	Route	Nominal Dose (mg/kg/day)	AUC_{0-last} (µg.h/mL)	*AUC* exposure ratio# *AUC*
Dog (beagle)	14 days WIL-609005	PO Capsule	460	0.045	0.3
	14 days WIL-609007	PO capsule	771	0.4	2
			1067	1.8	10
	14 days WIL-609002	PO Gavage	30	0.3-0.8	2-5
			60	0.06-0.6	0.3-3
			120	0.7	4
	3 months WIL-609006	PO gavage	108	1.6	9
			364	0.3	2
			1038	1.25	7
Human healthy volunteers	Single dose	PO	[400 mg]	0.172	

= animal:human plasma AUC0–24 h ; ND-not detected in plasma

Table 7. Relative exposure to the fidaxomicin metabolites Tiacumicin C and F after oral fidaxomicin

Species	Study duration (number)	Dose mg/kg /day	Analyte	C_{max} µg/ mL	AUC_{0-last} µg.h/mL	*AUC* exposure ratio C_{max}	*AUC*
Dog beagle PO	3 months (WIL-609006)	1038 [a] *N*	Tiacumicin C	0.056	0.174	-	-
			Tiacumicin F	0.156	0.574	6	3
Human healthy volunteers PO	steady state (10 days)	[400 mg]	Tiacumicin C	ND	ND		
			Tiacumicin F	0.0255	0.172		

ND -not detectable. a Doses not corrected for body weight during the study. The doses estimated in mg/kg using the weight recorded in Week 13: (♂ 10.3 kg, ♀: 8.4 kg)

Table 8. Relative concentration of fidaxomicin and OP-1118 in the gastrointestinal tract in dogs versus humans

Study	Nominal Dose mg/kg/day	Concentration in faeces µg/g		Conc. ratio (dog: human)	
		Fidaxomicin	OP-1118	Fidaxomicin	OP-1118
WIL609005	58	1418- 1880	28- 48	1-2	0.04 – 0.07
WIL609005	144	3595 - 8700	78 - 140	3-8	0.1-0.2
WIL609006	216	282- 5160	48 - 225	0.3-5	0.07-0.3
WIL609006	346	175 - 38500	49 - 372	0.2 -35	0.07-0.5
WIL609005	461	7300 - 10920	118 - 214	7-10	0.2-0.3
WIL609007	824	5658 - 12050	84 - 159	5-11	0.1-0.2
WIL609006	1038	16985 - 182500	219 - 1133	16-167	0.3-1.6
WIL609007	1238	10070 - 22100	137 - 435	9-20	0.2-0.6
Human studies: Phase IIA, 101.1.C.003 101.1.C.004	[2×200 mg] (10 days)	1091	696		

Table 9. Relative dose of fidaxomicin in the gastrointestinal tract in monkeys versus humans

Species	Study duration (number)	Dose mg/day	Dose mg/kg/day	*Dose* ratio
monkey cynomolgus PO	3 months (WIL-609006)	-	11	1
			34	4
		-	102	13
Human healthy volunteers PO	steady state (10 days)	[400 mg]	8[a]	

[a] Calculated for a 50 kg human

Major toxicities

No systemic toxicities were observed after oral treatment with fidaxomicin. Abnormal excreta (soft and discoloured faeces, and/or diarrhoea) and/or emesis were observed in dogs at high doses but are thought to be related to the extremely high doses of fidaxomicin that were administered, reaching ~3% of the daily food intake in the pivotal dog study. The No observable Adverse Effect Level (NOAEL) after PO dosing ≥ 90 mg/kg/day in rats, ≥ 9600 mg/day (~1038 mg/kg/day) in dogs and ≥ 101 mg/kg in monkeys resulting in

systemic exposure below level of quantification in rats, and 137 and 9 times that expected clinically, in dogs and monkeys respectively.

No sign of local toxicity of fidaxomicin or OP-1118 was observed in rats and dogs after oral dosing despite high concentrations reached in the gastrointestinal tract of dogs. Macroscopic and microscopic examination showed no treatment related effect on gastrointestinal tissue (stomach, duodenum, jejunum, ileum, caecum, colon or rectum). Additionally, no effects on food consumption, body weights or other clinical signs of gastrointestinal toxicity were observed apart from the abnormal excreta/emesis that was not considered related to the toxicity of the active ingredient. In monkeys, minimal to mild increased numbers of lymphocytes and plasma cells were observed at 4 fold the clinical intended dose based on a mg/kg basis, suggesting an immunogenic effect. Whether this effect occurred in response to treatment or in response to a mild increase in numbers of protozoa that are typically not considered harmful in the gastrointestinal tract of this species is not entirely clear. It could not be determined if fidaxomicin induced local GI-irritation in monkeys. The NOAEL for the immunogenic effect (11 mg/kg/day) was similar to the clinically expected dose of 8 mg/kg/day. However, given the minimal to mild nature of findings only occurring at higher than expected clinical doses and the absence of significant findings in other species this is unlikely to be clinically relevant.

At the clinically intended dose of 2x200 mg/day, fidaxomicin is not expected to cause significant systemic or local toxicity in humans based on animal data.

Genotoxicity

The potential genotoxicity of fidaxomicin was investigated using the standard battery of tests and some additional testing. The studies were conducted according to ICH guidelines and under GLP conditions. Concentrations/doses used were appropriate. Tests included bacterial reverse mutation and chromosomal aberration in vitro as well as the rat in vivo micronucleus test and comet assay that specifically investigated genotoxic effects on duodenal and liver cells after oral dosing. The use of male animals only in the main studies was acceptable since no sex differences in metabolism were detected. In addition to fidaxomicin, the main metabolite, OP-1118, was tested for bacterial mutation and chromosomal aberration in vitro. Separate in vivo assays for OP-1118 were not required since the main metabolite is rapidly formed in vivo in rats, dogs and humans. All assays were appropriately validated and returned negative results with one exception. An in vitro chromosome aberration assay was positive for structural aberrations in the absence of S913 metabolic activation, which was reproducible. The effect was only observed at very high concentrations (125 µg/mL) that induced 39% cell growth inhibition. However negative findings were returned in the presence of S9 at higher concentrations. The result is not regarded to be clinically relevant. In support of this, high exposures to fidaxomicin induced no local or systemic genotoxicity in all of the in vivo assays. Fidaxomicin did not increase DNA breaks in duodenal tissue after daily oral doses up to 2000 mg/kg which was associated with 8 and 0.9 times the clinical fidaxomicin and OP-1118 concentration in faeces. Systemically, fidaxomicin did not increase DNA breaks in liver tissue at plasma exposures 38 and 12 times the clinical Cmax and did not increase the frequency of micronuclei in rat polychromatic erythrocytes after IV dosing with 75 mg/kg fidaxomicin. Therefore, based on a weight of evidence approach with negative *in vivo* findings fidaxomicin is considered to have low genotoxic potential.

[13] Drugs sometimes require metabolic activation in order to become mutagenic. The S9 fraction is an organ tissue homogenate (usually rat liver) and contains cytochrome P450 isoforms (Phase I metabolism) and other enzyme activities. Since the metabolic enzymes of the bacteria used in the Ames test differ substantially from those present in mammals, the addition of the S9 fraction gives the Ames test a better assessment of the mutagenic potential of the drug and its metabolites in mammals.

Carcinogenicity

No carcinogenicity studies were submitted. This is considered acceptable due to the overall negative genotoxicity results, low bioavailability and the short intended treatment duration.

Reproductive toxicity

Submitted reproductive toxicity studies covered fertility and early embryonic development (rats) and embryofetal development (rats, rabbits) but no pre-post natal development were submitted. This is acceptable considering the proposed short duration of treatment. Studies were conducted after intravenous administration to maximise systemic exposure. The number of animals and the timing and duration of treatment were appropriate. The dosing vehicle was 1% Solutol HS-15/phosphate buffered saline in all studies, administered at a dose volume of 10 mL/kg except in the embryofetal development study 1069-007, where a 20 mL/kg dose volume was used. Due to the low aqueous solubility of fidaxomicin, the highest achievable nominal dose was 7.5 mg/kg/day using 10 mL/kg, the maximum possible dose volume for longer term IV studies in rabbits. Group sizes and treatment periods were appropriate.

Table 10. Relative exposure (fidaxomicin)

Species	Study	Nominal Dose (mg/kg/day) IV		$AUC_{0-¥}$ (µg.h/mL)	Exposure ratio#
Rat (SD)	Fertility (1069-013)	♂ *Day 28*	1	0.5	6
			4	3	37
			7.5	4.8	59
		♀ *GD7*	1	0.2	2
			4	1.5	18
			7.5	5.1	62
	Embryofetal development (1069-007)	♀ *GD17*	4	1.2	15
			8	5.2	64
			15	9.4	115
Rabbit (NZW)	Embryofetal development (1069-018)	♀ *GD18*	2	NC	-
			4	2.2	27
			7.5	2.6	32
Human (healthy volunteers)	steady state	[400mg]		0.0817[a]	–

= animal: human plasma AUC0–last; aAUC0-24h; NC - not calculated

Table 11. Relative exposure (fidaxomicin main metabolite OP-1118)

Species	Study	Dose (mg/kg/day) IV		$AUC_{0\text{-last}}$ (µg.h/mL)	Exposure ratio# *AUC*
Rat (SD)	Embryofetal development	♀ *GD 17*	4	1.3	8
			8	2.8	16
			15	6.7	39
Rabbit (NZW)	Embryofetal development	♀ *GD 18*	2	4	23
			4	11.2	65
			7.5	25.2	147
Human (healthy volunteers)	steady state	[400mg]		0.172[a]	–

= animal: human plasma AUC0–last, aAUC 0-24h; Doses corrected for purity: WIL- 609008

High multiples of the clinical AUC were obtained in the pivotal studies.

Placental transfer was not investigated and is unlikely since after oral administration systemic levels of both fidaxomicin and its main metabolite OP-1118 are very low. The ability of fidaxomicin to cross the blood placenta barrier is likely further reduced since it is a substrate for the efflux pump P-glycoprotein and both compounds possess low permeability. Excretion into milk was not investigated.

Male and female fertility and early embryonic development were unaffected in rats treated up to 7.5 mg/kg IV, estimated to be 60 fold the anticipated clinical AUC exposure to fidaxomicin. Exposure to the metabolite OP-1118 was not assessed in this study; however exposure ratios based on C_{max} after administration of 7.5 mg/kg IV were estimated to be up to 106 fold the clinical C_{max} exposure in males using Toxicokinetics from a safety pharmacology study. Since no consistent sex differences were observed during the studies the exposure is assumed to be similar in females. No effects were observed on ovulation, implantations, pre- and post implantation loss, normally developing implants and resorptions. The No Observable Effect Level (NOEL) is 7.5mg/kg/day IV.

Embryofetal development was unaffected after repeated IV administration of fidaxomicin to rats (≤ 15 mg/kg/day, 115 relative AUC exposure) and rabbits (≤ 7.5 mg/kg/day, 32 relative exposure). These doses were associated with exposures to the main fidaxomicin metabolite that reached 39 (rat) and 147 fold (rabbit) the anticipated clinical AUC for this metabolite in humans.

Pregnancy classification

The sponsor has proposed Pregnancy Category B 1.

Category B1 is intended for Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Category B1 is considered appropriate considering the absence of animal findings in adequately conducted embryofetal development studies, the clinical reproductive toxicity is not evaluated in this nonclinical report.

Local tolerance

No studies investigating local tolerance specifically were submitted. Since fidaxomicin absorption is low, the main site of local exposure is the gastrointestinal tract. The rat and dog repeat dose toxicity studies showed no sign of fidaxomicin related local gastrointestinal irritation. Local irritation in response to fidaxomicin in the repeat dose monkey study is uncertain, but could not be excluded (see *Repeat dose toxicity*).

Impurities

Twenty chemicals that required qualification were identified as impurities in fidaxomicin drug substance or drug product. The proposed specification limits for all the impurities exceeded the ICH qualification threshold. Some of these impurities, including the major impurity OP-1405, were qualified through toxicological studies. All impurities were qualified genotoxicologically in an *in vivo* assay for liver and duodenal cell DNA damage.

The levels of the ten impurities were too low to be detected in the repeat dose study and are therefore not qualified from a toxicological point of view. Considering the low systemic absorption of fidaxomicin (the largest fraction is contained in the faeces), the short duration of the clinically proposed treatment and the potential severity of the condition, this may be acceptable on clinical grounds.

Paediatric use

No nonclinical data investigating the use of fidaxomicin in children was submitted. According to the recommended dosage in the draft Product information document Dificid is not recommended for use in children.

Nonclinical Summary

- The sponsor has conducted adequate studies on the nonclinical pharmacology, pharmacokinetics and toxicology of fidaxomicin. All pivotal studies were conducted under GLP conditions.
- Fidaxomicin is a narrow spectrum antibiotic, it shows moderate activity towards most Gram positive bacteria and is bactericidal against Clostridium difficile. The mechanism of action is inhibition of transcriptional initiation, by inhibition of RNA polymerase. The mechanism of RNA polymerase inhibition appears to be distinct from other RNA polymerase inhibitors (rifamycins). The main metabolite of fidaxomicin, OP-1118, contributes to the overall antibacterial activity of the product. Bactericidal activity of fidaxomicin was shown to be time dependent and not concentration dependent above the MIC. Fidaxomicin effectively prevented lethal Clostridium difficile infection in clindamycin pretreated hamsters. Efficacious doses were below the proposed clinical dose.
- Secondary pharmacology studies were not conducted. Safety pharmacology studies covered CNS, respiratory and cardiovascular system. No fidaxomicin related effects were observed at exposures much higher than anticipated clinically.
- Fidaxomicin was characterised as a BCS Class IV compound and possesses low solubility and permeability. Consequently systemic absorption is low in all species, which is desired since the site of action is the gastrointestinal tract. Despite efforts to increase absorption in animal studies bioavailability was <3%. The main metabolite, OP-1118, was also rapidly generated in all tested species including humans. Fidaxomicin did not accumulate with repeated dosing and no sex differences were observed. Plasma protein binding was high in all species. Excretion following oral dosing occurred mainly via the faeces as unchanged drug and the main metabolite OP-

1118, mainly due to poor absorption. Fidaxomicin was shown to act as an inhibitor and substrate for P-glycoprotein.

- Fidaxomicin showed a low order of acute toxicity.
- Pivotal repeat dose studies were conducted in rats (1 month), dogs (3 months) and monkeys (1 month). Systemic exposure to fidaxomicin and OP-1118 achieved in the dog and monkey toxicity studies were adequate. Fidaxomicin was well tolerated. No signs of fidaxomicin induced local gastrointestinal toxicity were observed in rats and dogs. In monkeys, minimal to mild increased numbers of lymphocytes and plasma cells were observed at 4 fold the clinical intended dose based on a mg/kg basis. It cannot be excluded that this was a treatment related effect but it is considered unlikely to be clinically relevant.
- Fidaxomicin was tested for potential genotoxicity using the standard battery of tests, with negative results in all in vivo assays. In vitro, fidaxomicin was negative for bacterial mutation but showed a positive result for chromosomal aberrations in Chinese hamster ovary cells at very high concentrations. Based on a weight of evidence analysis, fidaxomicin was considered to be non genotoxic. Due to the overall negative genotoxicity results, the intended short duration of treatment and low bioavailability, no carcinogenicity studies were conducted.
- Fidaxomicin did not affect fertility in rats or embryofetal development in rats and rabbits at exposures in excess of the clinically anticipated exposure. Pre- post-natal development, placental transfer and excretion into milk were not investigated, which is acceptable due to the negative embryofetal findings and the minimal oral absorption and short proposed duration of treatment of fidaxomicin.

Nonclinical conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- Fidaxomicin is a narrow spectrum antibiotic with bactericidal activity against Clostridium difficile with only moderate activity against other gram positive bacteria in vitro. Fidaxomicin effectively prevented lethal Clostridium difficile infection in clindamycin pretreated hamsters. Overall the nonclinical pharmacology studies supported the proposed dose and part of the proposed indication; The treatment of Clostridium difficile infection.
- Safety pharmacology studies revealed no clinically relevant hazards.
- Fidaxomicin was well tolerated in rats, dogs and monkeys.
- Fidaxomicin did not show genotoxic potential in animal studies. The lack of carcinogenicity studies is acceptable.
- Fidaxomicin did not show reproductive toxicity, pre and post-natal studies were not conducted.
- There are no major nonclinical objections to registration. However, not all of the specified impurities were toxicologically qualified. Considering the low systemic absorption of fidaxomicin (the largest fraction is contained in the faeces), the short duration of the clinically proposed treatment and the potential severity of the condition, this may be acceptable on clinical grounds.
- Amendments to the draft Product Information were recommended to the Delegate but these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

Clinical rationale

The rationale put forward by the sponsor for investigation of fidaxomicin for use in CDAD include the need for a narrow spectrum bactericidal agent against *Clostridium difficile* (*C. difficile*) with low potential for development of resistance or cross resistance and minimal systemic absorption.

Guidance

The TGA adopted EU guidelines include 'Points to consider on Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products' accessible from <http://www.tga.gov.au/pdf/euguide/ewp265599en.pdf>.

Contents of the clinical dossier

The clinical studies supporting this application comprise 1 food study, 1 single dose pharmacokinetics (PK) study and 1 multiple dose PK study. There are 3 drug-drug PK interaction studies. All PK studies were in healthy adult volunteers.

There is one Phase II dose selection study and two Phase III pivotal clinical trials. These three studies were carried out in adult patients with CDAD.

A study to ascertain absolute bioavailability of fidaxomicin has not been performed. A justification for this was included in the sponsor's submission. The factors supporting this course of action included local (non-systemic) mode of action, localised pathology for which usage is being sought, well-characterised and simple metabolic fate.

Paediatric data

This submission does not contain paediatric data.

Good clinical practice (GCP)

The clinical studies included in this submission are stated to have complied with the GCP and the applicable ethical standards of human research.

Pharmacokinetics

Evaluator's overall conclusions on pharmacokinetics

Fidaxomicin has simple pharmacokinetics and is not absorbed systemically to any clinically significant degree. The excretion is via faecal route as intact parent drug and its metabolite. Given the topical action within the gastrointestinal tract, low systemic bioavailability, absence of clinically relevant interaction for fidaxomicin exposure, the plasma pharmacokinetic features may thus not be critical in clinical practice. There is small food effect (lower bioavailability) which is also not clinically relevant. The effect on cyclosporine, digoxin and warfarin may be clinically important in CDAD patients and although no dose adjustments are recommended based on data, such co-administration should be monitored including measurement of plasma drug levels for these drugs.

Pharmacodynamics

Summary and evaluator's comment on pharmacodynamics

Fidaxomicin has narrow spectrum of antibacterial activity. It is bactericidal against *C. difficile in vitro* inhibiting RNA synthesis by RNA polymerase. Gram negative organisms both aerobic and anaerobic are intrinsically insensitive. It has variable activity against facultative and aerobic Gram positive bacteria. It has variable activity against Gram positive anaerobic bacteria.

Rate of resistance development to fidaxomicin has been shown to be low. It does not exhibit cross resistance to other classes of antibiotics.

The risk of development of bacterial (*C. difficile*) resistance to fidaxomicin is considered low but will require institution of organised resistance surveillance program if the drug is approved for marketing.

Efficacy

There were two identically designed pivotal efficacy studies to support the regulatory approval of this product; Studies 101.1.C.003 and 101.1.C.004 (Studies 003 and 004).

Evaluator's conclusions on clinical efficacy

The use of 200 mg fidaxomicin every 12 h was appropriate based on Phase II dose finding study. The two pivotal efficacy trials were appropriately designed. The follow up was complete especially with respect to the primary outcomes. The results, repeated in two separate and similarly designed double blind, active controlled studies, are considered reliable demonstration of efficacy of fidaxomicin over vancomycin in the treatment of CDAD.

Safety

Safety data were collected in all clinical studies included in the dossier.

Postmarket data

The total exposure estimate for the current aggregate reporting period based on overseas (US and some Canadian exposure) approval (27 May 2011 to 26 November 2011) is approximately 5414 patient-courses of therapy.

A total of 47 individual safety reports were received with a total of 121 reported events including 5 reports with a fatal outcome were received. The reports designated *serious and unlisted* included Infections and Infestations (9; most frequent PT was Clostridial infection [4]), Cardiac disorders (5; all PTs were n=1), Gastrointestinal disorders (5; all PTs were n = 1), and Investigations (5; most frequent PT was WBC count increased [2]). The most frequent serious unlisted PT was Clostridial infection (n=4). The most frequent non-serious unlisted PTs included diarrhoea (n=9), Clostridial infection (n=5) and *C. difficile colitis* (n=4).

Possible hypersensitivity reactions reported in the postmarketing setting and in Phase III trials were also reviewed. Overall, 20 cases of rash were identified searching both the global safety and clinical trial databases: 16/564 (2.8%) fidaxomicin treated patients experienced skin rash and 4 cases of rash were reported in spontaneous postmarketing reports. All 20 cases reported mild to moderate rash events that resolved on discontinuation with or without treatment.

Evaluator's comment on clinical safety

The safety dataset is limited comprises about 120 healthy adult volunteers exposed to fidaxomicin in pharmacokinetic studies and 52 healthy adult volunteers exposed to fidaxomicin in drug-drug interaction studies. Most of this experience was single dose exposure. A total of 612 adult CDAD patients (260 males; 352 females) including elderly (≥ 65 years old; n = 285) were exposed to fidaxomicin in the 3 Phase II and Phase III studies for treatment up to 10 days.

Another limitation in assessment of the adverse effects profile is the issue of confounding by the underlying disease especially with respect to effects on electrolytes, haematology and gastrointestinal adverse events. Placebo controlled data is not available.

Despite these limitations, it can be concluded due to the controlled nature of the data that the overall adverse effects profile of oral fidaxomicin is similar to oral vancomycin in the treatment of CDAD including deaths and serious adverse events (SAEs) although the pattern for SAEs is somewhat different in the two groups. For fidaxomicin, the haematological effects especially on white blood cells and effects on hepatic function (enzymes) will need further data for convincing attribution.

First round clinical summary and conclusions

First round assessment of benefits

The clinical efficacy of 10 day course of 200 mg oral fidaxomicin every 12 h was found to be similar (non inferior) to 10 day course of 150 mg oral vancomycin every 6 h in the treatment of CDAD with respect to the physician's assessment of clinical cure based on signs and symptoms of disease in particular diarrhoea (88% versus 86% and 88% versus 87% in the two trials).

However, fidaxomicin treatment provided clear advantage and was superior to the comparator vancomycin in preventing recurrence of disease within 4 weeks of completion of therapy (14% versus 26% respectively across both pivotal clinical studies).

The global cure rate which may be interpreted as sustained clinical response, that is, clinical cure without recurrence within 4 weeks was also statistically and clinically higher with fidaxomicin treatment than with vancomycin.

First round assessment of risks

Neutropenia in association with fidaxomicin may need to be monitored. The risk of development of resistance is considered low.

The evaluator also referred the Delegate to a Risk management Plan (RMP) evaluation but this discussion is beyond the scope of this AusPAR.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance is considered in favour of fidaxomicin use in the treatment of CDAD and provides potentially advantages over the currently approved drug vancomycin in this condition such as lower rate of recurrence within 4 weeks of treatment, narrower spectrum of activity low potential to affect resident gastrointestinal flora, simple pharmacokinetics and easier twice daily dosing regimen.

The fidaxomicin treatment also provides potential benefit of lower risk of contributing to antibiotic resistance since cross resistance with other antibiotic groups has not been observed and a lower risk of colonisation with vancomycin resistant enterococcus (VRE) observed the clinical study.

Second round evaluation of clinical data submitted in response to questions

The following further information was sought from the sponsor during course of the evaluation:

Question 1: Study OPT-80-1B-MD: it is not clear why no faecal OPT-80/Op-1118 were detected in 6 out 24 participants even though the samples seem to have been available for all participants. The sponsor is requested to provide comment.

Sponsor's response: No fidaxomicin concentrations were present in the faeces of 6 subjects because each group (3 groups) contained 2 placebo treated subjects.

TGA response: Noted.

Question 2. Study OPT-80-007 (cyclosporine interaction study): Although fidaxomicin is a substrate for P-gp, given the proposed recommendation that cyclosporine/fidaxomicin co-administration be allowed, has the effect of fidaxomicin on cyclosporine been studied or provide comment why the two way interaction is not considered applicable especially on multiple dosing?

Sponsor's response: Cyclosporine is a powerful P-glycoprotein (P-gp) inhibitor and the objective of this study was to determine the impact of P-glycoprotein inhibition on fidaxomicin pharmacokinetics. Fidaxomicin has been poorly characterised, however, as a test substrate for P-glycoprotein, and the importance of P-gp in its intestinal uptake is unclear. While cyclosporine has been reported to be a P-gp substrate[14], polymorphisms in MDR1 have not been shown to explain differences in pharmacokinetics of cyclosporine[15] and much of the variability is associated instead with polymorphisms in CYP3A4, suggesting that the latter is the major contributor to variability in bioavailability. Substrate-based drug interactions have been reported at the level of the kidney, in terms of increased nephrotoxicity in the presence of P-gp inhibitors in renal epithelial cells.[16] Because fidaxomicin has minimal absorption (ng/mL concentrations in the plasma, well below the μg/mL IC_{50} for inhibition of P-gp), this interaction is predicted to be irrelevant for fidaxomicin. Cyclosporine is metabolised by CYP3A4, and while fidaxomicin is a very weak inhibitor of CYP3A4, another DDI study (OPT-80-009) demonstrated no impact of fidaxomicin on the pharmacokinetics of CYP3A4 substrate midazolam. Thus, such an interaction was also considered unlikely. Because of the generally conflicting results reported in the literature as to the impact of P-gp on cyclosporine uptake, it was decided to use a more specific test substrate, digoxin, to evaluate the potential impact of P-gp inhibition. Administration with fidaxomicin had no clinically relevant impact on digoxin pharmacokinetics. It is worth noting that although cyclosporine pharmacokinetics were not compared in a crossover manner in this study (there was no cyclosporine-only dosing sequence), cyclosporine concentrations were measured in the presence of fidaxomicin dosing. Cyclosporine concentrations measured (C_{max}, 395 ± 95 ng/mL following a 200 mg dose) were similar to cyclosporine concentrations reported by others using an equivalent assay (Liquid Chromatography-Mass Spectrometry (LC-MS) rather than Enzyme-Linked Immunosorbent Assay (ELISA), which can cross-react with metabolites and overestimate concentrations), when adjusted for dose (after a 100 mg dose, C_{max} was 254 ± 85 ng/mL).[17]

[14]Fricker G. et al. (1996). Relevance of p-glycoprotein for the enteral absorption of cyclosporin A: in vitro -in vivo correlation. British Journal of Pharmacology 118, 1841-1847

[15] Haufroid V. et al The effect of CYP3A5 and MDR1 (ABCB1) polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenetics 2004, 14:147–154

[16] Anglicheau D. et al (2006). Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine–sirolimus interaction. Kidney International 70, 1019–1025

[17]Najib NM et al (2003). Comparison of two cyclosporine formulations in healthy Middle Eastern volunteers: bioequivalence of the new Sigmasporin Microoral and Sandimmun Neoral. European Journal of Pharmaceutics and Biopharmaceutics 55:67–70

TGA response: This reply was also quoted earlier in discussing interaction with cyclosporine. As noted earlier, this interaction (and with digoxin and warfarin) are small in quantitative terms but may be clinically significant in patient population under treatment. Although no dose adjustments are proposed but monitoring including therapeutic drug measurements on individual risk assessment basis may be required when fidaxomicin is given to these patients.

Question 3. Are any other interaction studies being done or planned such as co-administration with dabigatran?

Sponsor's response: No specific drug-drug interaction (DDI) studies are planned around P-gp, however, targeted pharmacovigilance activities include aggregate review of patients who are reported to have received concomitant p-gp inhibitors for identification of potential safety signals.

TGA response: Noted.

Question 4. Please confirm whether commercial formulation was used in Phase II and both Phase III trials. If not please outline the differences.

Sponsor's response: The commercial formulation (200 mg film coated tablet) was used in both Phase III studies (101.1.C.003 and 101.1.C.004). A 50 mg powder-filled capsule was used in study, OPT-80 Phase 2A.

TGA response: Noted.

Question 5. Study 101.1.C.003: It is not clear why a small number of patients had detectable levels of OPT-80 and OP-1118 in plasma prior to dosing on Day 1 of the study. Please provide comments.

Sponsor's response: Seven subjects in Study 003 had "pre-dose" levels above the quantification limit at the start of study. Of these, 1 had the first sampling time point on the second day of dosing, explaining the measurable concentration. The other 6 may be "post-dose" samples placed in "pre-dose" tubes, since:

- In two cases the "post-dose" sample was "missing" and two "pre-dose" tubes were received and analysed,
- In one case only one pre-dose sample was analysed but the post-dose sample was missing (although recorded as having been collected), and the last three are potentially duplicate post-dose samples inadvertently placed in predose tubes, as the fidaxomicin concentrations are virtually identical between the "predose" and "post-dose" samples; this suggests that these were duplicate samples inadvertently placed in pre-and post-dose tubes, rather than both being placed in post-dose tubes.
- While human error cannot be eliminated entirely in sample collection, these events are expected to have been very infrequent based on the rarity of the positive pre-dose samples (only 6 out of 265 pre-dose samples were positive.) Thus, these rare errors would have had no significant impact on the outcomes or conclusions of the pharmacokinetic analysis overall.

TGA response: Noted.

Question 6. Please provide Australian prevalence data for CDAD, if available. Please provide a copy of the Ferguson (2011)[18] paper referred to in the sponsor's assessment of risk of antibiotic resistance development. Has infection with virulent strain (NAP1/BI/027) been reported here? Has any data on epidemiological breakpoints become available?

Sponsor Response: The Ferguson, 2011 reference was provided with the current submission; in general, there are few studies of *C. difficile* incidence in Australia. Although this paper notes that there are limitations to the data captured (that is, reporting was voluntary, one site could not report data, and there was no central control regarding what stools were tested, what criteria were used for select stools for testing, or what tests were used), the estimated incidence they report is 18.0-35.8 cases per 100,000 population. NAP1/BI/027 has been reported in Australia, although the incidence is as yet unknown.[19], [20] An epidemiological cut off (ECOFF) value of 0.5 µg/mL was set up by European Committee on Antimicrobial Susceptibility Testing (EUCAST) based on MIC data from the two fidaxomicin clinical trials and from 5 other independent laboratories as listed below in Table 12.

Table 12. In vitro studies of Fidaxomicin MIC distributions against clinical C. difficile isolates.

Total	Distribution of MIC (µg/mL) Values											Total	MIC Range	MIC_{50}	MIC_{90}
				0.015	0.03	0.06	0.125	0.25	0.5	1	2				
101.1.C. 004 trial	0	0	9	20	28	75	144	90	24	1	0	391	0.007-1	0.125	0.25
101.1.C. 003 trial	0	2	5	17	37	112	156	95	9	0	0	433	0.004-0.5	0.125	0.25
Karlowsky, 2008	0	0	0	0	0	2	73	65	51	17	0	208	0.06- 1	0.25	0.5
Hecht, 2007	0	0	0	9	11	29	50	11	0	0	0	110	0.015-0.25	0.125	0.125
Finegold, 2004	0	0	0	0	0	7	11	3	1	0	1	23	0.06-2	0.125	0.25
Credito, 2004	-	-	-	12	0	3	2	1	0	0	0	18	≤0.016 - 0.25	≤0.016	0.125
Ackermann, 2004	117	49	21	16	1	3	0	0	0	0	0	207	≤0.0009-0.06	0.0019	0.0078

The rational for choosing 0.5 (in lieu of 1) µg/mL as ECOFF was based on the fact that isolates with MIC of 1 µg/mL were mostly observed in one laboratory in Canada.[21] Because of the generally high MIC range at this site (0.06-1 µg/mL) and the nearly exclusive localisation of the isolates with an MIC of 1 µg/mL to this single site, EUCAST could not rule out the possibility that the MIC values of 1 µg/mL reflected a slight but systematic bias to the MIC values at this site (despite quality control (QC) results that were within acceptable ranges). Since then, however, *C. difficile* isolates with MIC of 1 µg/mL

[18] Ferguson JK et al (2011). Clostridium difficile laboratory testing in Australia and New Zealand: national survey results and Australasian Society for Infectious Diseases recommendations for best practice. Pathology 00 p:1-6.
[19] Richards M. et al (2011). Severe infection with Clostridium difficile PCR ribotype 027 acquired in Melbourne, Australia. MJA 194: 369-371)
[20] Riley T.V. et al (2009). First Australian isolation of epidemic Clostridium difficile PCR ribotype 027. MJA 190: 706-708
[21] Karlowsky JA et al (2008). In Vitro Activity of OPT-80 Tested against Clinical Isolates of Toxin-Producing Clostridium difficile. Antimicrobial Agents and Chemotherapy 52(11) p. 4163–4165

have also been reported and identified during our ongoing surveillance study. The ongoing surveillance investigation is a postmarketing study that involves participation of six US centres and has so far resulted in testing of over 470 isolates from different geographic locations.[22]

TGA response: The ECOFF is recommended for inclusion in the Australian PI.

Question 7. Please provide comment on surveillance studies of C. difficile that are being planned internationally. Will surveillance program be instituted in Australia? This may have been included in the RMP in refer to RMP should be sufficient.

Optimer has, thus far, implemented surveillance in the US and is setting up surveillance in Canada (to begin in approximately first quarter of 2013), the two regions for which it is the marketing authorisation holder (MAH), Astellas Pharma Europe Ltd., the MAH in Europe, has initiated surveillance in Europe. STA is evaluating the best method to conduct surveillance in Australia (that is, either arrange for sentinel sites in Australia to submit toxin-positive stool samples/*C. difficile* isolates to an existing program, or alternatively initiate a new local program).

Second round benefit-risk assessment

Second round assessment of benefits

The expected benefits of treating CDAD with 10 day course of fidaxomicin (200 mg every 12 h) compared to vancomycin (125 mg every 6 h) remain unaltered that is, non-inferior clinical response at end of therapy (88% versus 86% and 88% versus 87% in the two pivotal trials respectively) and superior sustained efficacy in terms of recurrence at 4 weeks after completion of treatment (15% versus 25% and 13% versus 27% in the two pivotal studies respectively).

Second round assessment of risks

The expected risks and need for further collection of data such as incidence of neutropenia remain unchanged.

Drug-drug interactions assessed during the development indicate only small magnitude of changes in pharmacokinetic on use with P-gp or CYP substrates. However, these may be meaningful in clinical practice and for narrow therapeutic index drugs such as cyclosporine, digoxin and warfarin, concomitant use with fidaxomicin may need monitoring.

The risk of development of resistance is low but not negligible and will require systematic surveillance.

Second round assessment of benefit-risk balance

Overall, the risk-benefit balance is in favour of benefit especially in light of sustained efficacy at 4 weeks compared to vancomycin and the postulated low potential for cross-resistance.

[22] Snydman DR et al A US Based National Sentinel Surveillance Study for the Susceptibility and Epidemiology of Clostridium difficile Associated Diarrheal Isolates: Baseline CY 2011. Powerpoint presentation.

Second round clinical summary and conclusion

Vancomycin is the currently only approved antibiotic for use in the treatment of *Clostridium difficile* Associated Diarrhoea (CDAD), although a number of other antibiotics such as metronidazole are used off label in clinical practice. Oral vancomycin acts locally whereas metronidazole is absorbed systemically.

The evidence of clinical efficacy of fidaxomicin presented in the sponsor's submission relied on the two pivotal clinical efficacy trials. Both were similarly designed, active (oral vancomycin) controlled, randomised, double blind trials in adult CDAD patients and successfully established non-inferiority of 10 day course of 200 mg oral fidaxomicin every 12 h to 150 mg oral vancomycin every 4 h with respect to clinical cure (physician ascertained resolution of signs and symptoms of CDAD based on clinical examination and patient kept daily diary). The trials were well planned there were no identifiable critical shortcoming in design or execution. The non-inferiority was tested using both modified Intention-to-Treat (ITT) (88% versus 86% and 88% versus 87% respectively in fidaxomicin and vancomycin groups in the two trials) and Per protocol (PP) statistical populations and the lower side 95% confidence interval for the treatment difference fell safely within the predefined maximum tolerable inferiority margin.

Furthermore, fidaxomicin was statistically and clinically superior to vancomycin with respect to prevention of recurrence of CDAD (relapse within 28 days of competing treatment) of disease and higher global cure (clinical cure without relapse up till 28 days after completion of therapy).

Where the evidence for efficacy is considered reliable and confirmatory, the dataset for safety evaluation is too small (about 565 fidaxomicin treated patients in the 2 pivotal trials) to enable full safety characterisation of the drug. Based on the limited data in this submission, the adverse effects profile of fidaxomicin treatment was similar to the comparator vancomycin.

Other advantages of fidaxomicin include simple pharmacokinetics, local action without significant systemic absorption, long post antibiotic effect (although its significance is unclear), lack of CYP450 interactions, narrow spectrum of antimicrobial activity, lack cross resistance to other antibiotics and expected low risk of development of resistance.

Fidaxomicin achieves very high faecal levels; many thousands of times it MIC_{90} value against *C. difficile*. However, a relationship between faecal levels, MIC and clinical failures was not established in the clinical efficacy trials.

Based on these findings, the evaluator agreed that a first line indication is appropriate. However, the sponsor's proposed indication which includes '*reducing the risk of recurrence when used for treatment of CDI*' is not supported.

The evaluator agreed that fidaxomicin treatment was satisfactorily shown to have led to lower rate of recurrence within 28 days of completing treatment compared to vancomycin (15% versus 25% and 13% versus 27%) and this is the most important efficacy benefit of fidaxomicin over vancomycin. However, this is more appropriate a measure of sustained efficacy or alternatively more appropriate timepoint for measurement of clinical cure rather than prevention of recurrence.

A comprehensive assessment of risk of development of resistance was provided. The risk appears low but resistance surveillance will need to be instituted if the drug is given marketing approval.

Second round recommendation regarding authorisation

It is recommended that the sponsor's submission to register fidaxomicin (200 mg) tablets be approved for the following therapeutic indication and usage guidelines:

Fidaxomicin is indicated for the treatment of Clostridium difficile Associated Diarrhoea (CDAD) in adults.

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 diagnosed to be caused by Clostridium difficile.

The recommended dose is 200 mg administered twice daily for 10 days.

Dificid can be taken before, during or after meals.

No dose adjustment is needed for elderly patients, patients with renal insufficiency, hepatic impairment or patients undergoing dialysis.

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

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is summarised in Table 13 below.

Table 13. Summary of ongoing safety concerns

Identified risks	None
Potential risks	Development of microbial resistance to fidaxomicin Treatment failure/Lack of effect Decreases in WBC, neutrophil, lymphocyte counts Gastrointestinal haemorrhage Hepatic laboratory value abnormalities Blood uric acid increased Hypophosphatemia QT-interval prolongation AEs Hypersensitivity
Missing information	**Potential populations at risk:** Patients with severe renal impairment Patients with severe and moderate hepatic impairment Patients with multiple recurrences of CDI Patients receiving repeated or extended fidaxomicin treatment courses Patients with inflammatory bowel disease Patients with life threatening or fulminant CDI, including pseudomembranous colitis Patients who are pregnant or lactating Paediatric patients Patients in whom potent inhibitors of P-gp are administered **Other missing information:** Impact of fidaxomicin on intestinal efflux/uptake transporters (BCRP, MRP2, OATP2B1)

OPR reviewer comment

This summary of the Ongoing Safety Concerns is essentially the same as that submitted in Europe, except for the addition of the Important missing information: '*Patients with multiple recurrences of CDI*'.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities are proposed to monitor all the specified Ongoing Safety Concerns. A comprehensive description of a routine pharmacovigilance system, including the responsible company and its sub-contractors, has been provided. However it has been established that none of these entities operate in Australia, only in Europe. In addition the sponsor states: *"Prior to commencement of supply, an Australian Qualified Person for Pharmacovigilance (AU-QPPV) will be employed by either the marketing partner chosen to distribute DIFICID in Australia or its designate. Details will be advised to the Office of Product Review by the Australian sponsor in due course."*

An additional pharmacovigilance activity is proposed to further characterise the Important potential risk: '*Development of microbial resistance to fidaxomicin*'. An international post-marketing surveillance program to monitor isolated strains of *C. difficile* for changes in antimicrobial resistance patterns is being conducted over a five year period

in the US. A final US protocol and an interim US report, as well as a draft EU protocol, were provided in the sponsor's correspondence dated 3 May 2012. An assurance has been provided that a study report and conclusions based on analysis of data will be prepared on a yearly basis and progress updates will also be shared at regular intervals.

For the Important missing information: '*Paediatric patients*', the following Paediatric Investigational Plan is proposed:

- An US multi-centre, open-label Phase IIA study to determine the safety and pharmacokinetics of fidaxomicin oral suspension and tablets taken very 12 h (q12h) for 10 days in paediatric patients aged 2 to less than 18 years with CDI. Protocol OPT-80-206 was provided in the sponsor's correspondence dated 3 May 2012, but no anticipated study completion date was reported.
- A planned multi-centre, open-label, randomised, parallel group Phase III study to compare the safety and efficacy of fidaxomicin oral suspension and tablets taken q12h, with vancomycin oral suspension and capsules taken every 6 h (q6h), for 10 days in paediatric patients aged 2 to less than 18 years with CDI. A draft protocol synopsis (OPT-80-206) was provided in the sponsor's correspondence dated 3 May 2012.
- A planned multi-centre, open-label, randomised, parallel group Phase III study to compare the safety and efficacy of fidaxomicin oral suspension and tablets taken q12h, with vancomycin oral suspension and capsules taken q6h, for 10 days in paediatric patients aged 1 to less than 24 months with CDI. A draft protocol synopsis (OPT-80-206) was provided in the sponsor's correspondence dated 3 May 2012.
- An ongoing observational, non-interventional study being conducted in Europe and North America to determine the role of Clostridium difficile in the pathogenesis of disease observed neonates and to investigate the feasibility of a potential study to evaluate safety, efficacy and PK of FDX oral suspension in neonates with CDI (The DAISY Study). Protocol 2819CL0204 was provided in the sponsor's correspondence dated 3 May 2012. Anticipated study completion is reported as first quarter of 2013.
- Depending upon the outcome of Protocol 2819CL0204, a study to evaluate the safety, efficacy and PK of FDX oral suspension in neonates with CDI is planned. A draft protocol synopsis was provided in the sponsor's correspondence dated 3 May 2012.

For the Important missing information: '*Patients with multiple recurrences of CD*I', a US Phase IIIb, multi-centre, double-blind, randomised, parallel group study to assess treatment effect of Fidaxomicin versus Vancomycin in subjects with single or multiple recurrences of CDI is to be apparently conducted. Protocol OPT-80-301 was provided in the sponsor's correspondence dated 3 May 2012, but no anticipated study completion date was reported.

For the Important missing information: '*Patients receiving repeated or extended fidaxomicin treatment courses*', a planned multi-national, multi-centre, open-label study to examine the safety and efficacy of extended treatment with fidaxomicin in subjects with recurrence of *Clostridium difficile* Infection previously treated with Fidaxomicin is to be conducted in Europe. Protocol 2819CL2001 was provided in the sponsor's correspondence dated 3 May 2012. The reported study period is from third quarter of 2013 to first quarter of 2016.

For the Important missing information: '*Impact of fidaxomicin on intestinal efflux/uptake transporters (BCRP, MRP2, OATP2B1)*', the following *in vitro* studies on intestinal efflux transporters have been completed:

- Interaction Studies of Fidaxomicin and its metabolite OP-1118 with the human uptake transporter OATP2B1 (OATP-B)

- Interaction Studies of Fidaxomicin and its metabolite OP-1118 with the human uptake transporter BCRP and MRP2.

Final study reports were provided in the sponsor's correspondence dated 3 May 2012.

A planned drug utilisation study of the use of oral fidaxomicin in the clinical setting is to be conducted in Europe. This is multi-centre, multinational, post-authorisation, retrospective chart review will extract exposure data collected from pharmacy prescriptions on a total of 500 consecutive subjects. The primary objective of this study is to assess the use of fidaxomicin in ordinary, routine clinical setting. Particularly, the number of patients with inflammatory bowel disease (IBD) exposed to fidaxomicin in routine clinical practice will be examined. Secondary objectives are to collect further safety data on fidaxomicin in the clinical setting and the use of fidaxomicin related to indication, dose and duration. Protocol 2819CL2002 was provided in the sponsor's correspondence dated 3 May 2012. The reported study period is from the third quarter of 2013 to the first quarter of 2015.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The description of the routine pharmacovigilance system is considered to be irrelevant to the Australian context. In light of the change in sponsorship this section of the Australian (AU) RMP should be completely re-written demonstrating consistency with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).* In addition details of the person responsible for the activities in the AU RMP within the sponsor company should be provided. It is expected that this will usually be the Australian pharmacovigilance contact person.

In principle there is no objection to the proposed additional pharmacovigilance activities. Nevertheless it is not clear if any of the specified studies will also be conducted in Australia. This is particularly significant for the planned drug utilisation study if it is to be representative of drug utilisation in Australia and the international postmarketing surveillance program to monitor changes in antimicrobial resistance patterns in Australia. The sponsor should state definitively if any of the specified studies are also to be conducted in Australia and if so provide for review at least draft Australian protocols for these studies.

The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of this study, to be outlined in the RMP (see below), will be expected in future Periodic Safety Update Reports (PSURs).

As per the Template for EU RMP, Section 2.4: '*Overview of planned or on-going studies*' of the AU RMP should be re-written to include required information, such as planned dates for submission of interim and final data. Similarly Section 2.6: '*Summary of outstanding actions, including milestones*' of the AU RMP simply states: *"Not applicable."* This is patently incorrect and should be re-written to include required information, such as ongoing and planned milestones and timelines.

In addition the nonclinical and clinical aspects of the Safety Specifications (SS) remain subject to the evaluation by the Toxicology area of the TGA's Office of Scientific Evaluations (OSE) and Office of Marketing Authorisation (OMA) respectively.

Risk minimisation activities

Routine risk minimisation activities will comprise labelling, including special Warning & Precaution statements, interactions with other medicines and/or *"other relevant sections"* for only the Important potential risk: '*Development of microbial resistance to fidaxomicin*'

and all the specified Important missing information, except for '*Patients with multiple recurrences of CDI*' for which no risk minimisation activity is proposed.

OPR reviewer comment

As previously mentioned, the sponsor has not provided any detail about the proposed routine risk minimisation activities for the specified Important potential risks, besides '*Development of microbial resistance to fidaxomicin*'. Consequently no assessment of this aspect of the AU RMP can be made until such detail is provided.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft product information document be revised as follows:

- For the Important missing information: '*Patients receiving repeated or extended fidaxomicin treatment courses*', no statement about the lack of data availability or advice about the use of caution in this population can be found. Appropriate information and advice should be included or compelling justification for the absence of such routine risk minimisation should be provided.
- For the Important missing information: *'Patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis)' & 'Patients with life threatening or fulminant CDI, including pseudomembranous colitis', the following wording has been proposed: "There are no clinical data in subjects with concomitant inflammatory bowel disease and very little data in subjects with pseudomembranous colitis. DIFICID should be used with caution in these patients."* It is suggested that the following wording from the currently approved EU Summary of Product Characteristics (SmPC) be adopted instead for clarity: *"Due to limited clinical data, fidaxomicin 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. Fidaxomicin should be used with caution in these patients due to the risk of enhanced absorption and potential risk of systemic adverse reactions."*
- For the Important missing information '*Co-administration of potent inhibitors of P-gp', the 'Drug-Drug interactions*' sub-heading of the '*Interactions with other medicines*' section of the draft Australian Product Information concludes that *"..., Dificid may be co-administered with P-gp inhibitors and no dose adjustment is recommended."* However, this is inconsistent with the currently approved SmPC which states: *"Co-administration of potent P-glycoprotein inhibitors such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended".* The sponsor should adopt the corresponding information and conclusions found in the currently approved SmPC or provide compelling justification to the contrary.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

First round summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the draft product information and consumer medicine information documents should NOT be revised until the Delegates Overview has been received:

- Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated information request and/or the nonclinical and clinical evaluation

reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Australian Risk Management Plan, and any specific information needed to address this issue in the AU RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the AU RMP.

- The description of the routine pharmacovigilance system is considered to be irrelevant to the Australian context. In the light of the change in sponsorship this section of the AU RMP should be completely re-written demonstrating consistency with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).* In addition details of the person responsible for the activities in the AU RMP within the sponsor company should be provided. It is expected that this will usually be the Australian pharmacovigilance contact person.
- In principle there is no objection to the proposed additional pharmacovigilance activities. Nevertheless it is not clear if any of the specified studies will also be conducted in Australia. This is particularly significant for the planned drug utilisation study if it is to be representative of drug utilisation in Australia and the international postmarketing surveillance program to monitor changes in antimicrobial resistance patterns in Australia. The sponsor should state definitively if any of the specified studies are also to be conducted in Australia and if so provide for review at least draft Australian protocols for these studies.
- The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of this study, to be outlined in the RMP (see below), will be expected in future PSURs.
- As per the Template for EU-RMP, Section 2.4: '*Overview of planned or on-going studies*' of the AU-RMP should be re-written to include required information, such as planned dates for submission of interim and final data. Similarly Section 2.6: '*Summary of outstanding actions, including milestones*' of the AU-RMP simply states: *"Not applicable."* This is patently incorrect and should be re-written to include required information, such as ongoing and planned milestones and timelines.
- The sponsor's conclusion that no additional risk minimisation activities are necessary at this time is generally consistent with the assessment of a similar application submitted in Europe. Nevertheless the nonclinical and clinical aspects of the SS remain subject to the evaluation by the Toxicology area of the OSE and by the OMA respectively.
- Section 3.1: '*Summary of routine risk minimization*' of the AU RMP, should be re-written to include required information for all the Important potential risks, not just for '*Development of microbial resistance to fidaxomicin*'. Similarly Section 5: '*Summary of the risk management plan*' of the AU RMP should also be amended.
- For the Important missing information: '*Patients receiving repeated or extended fidaxomicin treatment courses*', Section 3.1: '*Summary of routine risk minimization*' of the AU RMP states: *"CCDS and Australian Product Information states lack of data availability and advise use of caution in this population."* In conjunction Section 5: 'Summary of the risk management plan' of the AU RMP states: *"Warnings and Precautions section and/or other relevant sections of CCDS and Australian Product Information".* Such information and advice cannot be found in the draft Australian PI. Either these sections of the AU RMP should be amended or appropriate information and advice should be included in the draft Australian Product Information.

- The EU guideline adopted in Australia, namely Requirements for Risk Management Systems (pp 36-55, 96-101 and 202-203 of the Rules 2008, Vol. 9A)[23] states that the sponsor needs to take into account potential reasons for medication error. The naming, presentation (for example, size, shape and colouring of the pharmaceutical form and packaging), instructions for use (such as regarding reconstitution, parenteral routes of administration, dose calculation), and labelling are among the items to be considered. The need for visual (or physical) differentiation between strengths of the same medication and between other medicinal products commonly administered or taken at the same time should be discussed. When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Consideration should be given to the prevention of accidental ingestion or other unintended use by children. Consequently Section 3.2: 'Potential for medication errors' of the AU RMP should be amended accordingly.
- As previously mentioned, the sponsor has not provided any detail about the proposed routine risk minimisation activities for the specified Important potential risks, besides 'Development of microbial resistance to fidaxomicin'. Consequently no assessment of this aspect of the AU RMP can be made until such detail is provided.
- In regard to the proposed routine risk minimisation activities, a number of amendments to the draft PI were recommended to the Delegate but the details of these are beyond the scope of this AusPAR (see Response from Sponsor below).

Second round evaluation of the sponsor's response to the RMP evaluation

In summary the sponsor has adequately addressed all OPR recommendations, except for the following:

- The sponsor has stated that currently there is no proposal to conduct in Australia any of the specified studies in the Pharmacovigilance Plan, including the post-marketing surveillance program to monitor changes in antimicrobial resistance patterns (see *TGA Recommendation 3*). However, this is inconsistent with the sponsor's response quoted in the clinical evaluation report (CER) dated 25 October 2012, which states: *"STA is evaluating the best method to conduct surveillance in Australia (i.e. either arrange for sentinel sites in Australia to submit toxin-positive stool samples/C. difficile isolates to an existing program, or alternatively initiate a new local program)."* Furthermore the clinical evaluator has recommended that the risk of development of resistance will require systematic surveillance. This was supported by TGA's Advisory Committee on the Safety of Medicines (ACSOM) advice that the implementation of an Australian specific study to monitor changes in antimicrobial resistance patterns is important from a public health perspective. Consequently this remains an outstanding recommendation which the sponsor must address in an appropriate manner, preferably before this application is approved.
- The sponsor has stated that Sections 3.1 and 5 of the AU RMP have now been duly modified to include required information for all the Important potential risks. This information indicates that routine risk minimisation is included in the *Warnings* and *Precautions* sections of the Australian PI for all the Important potential risks. However for the majority of these Ongoing Safety Concerns no such information in the Australian PI can be found and therefore cannot be assessed (see *TGA Recommendation 7 and 10*). A similar situation continues to exist for the Important missing information: '*Patients receiving repeated or extended fidaxomicin treatment courses*' (see *TGA Recommendation 8*).

[23] <http://www.tga.gov.au/pdf/euguide/vol9riskmmt.pdf>

- In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft PI be revised but the details of these are beyond the scope of this AusPAR. The sponsor has made no material comment in relation to these recommendations to the Delegate. Consequently they remain outstanding.
- In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the OPR recommendations. The sponsor has made no material comment in relation to this recommendation to the Delegate. Consequently it remains outstanding.

In addition the CER dated 25 October 2012, the clinical evaluator has stated that neutropenia in association with fidaxomicin may need to be monitored and concluded that there is a need for further collection of data such as incidence of neutropenia. Such information cannot be derived from routine pharmacovigilance; consequently it would appear that additional pharmacovigilance will need to be proposed for the Important potential risk: '*Decreases in WBC, neutrophil and lymphocyte counts*', preferably before this application is approved.

Ratified advice from the 14th meeting of ACSOM also provided the following additional advice: *"The committee advised that enhanced pharmacovigilance should be undertaken for the high risk subpopulations that were omitted from the clinical studies. For example it was considered likely that fidaxomicin will be used in patients with inflammatory bowel disease (IBD); even though patients with IBD were not included in the efficacy studies. There is potential that the intestinal barrier will be more permeable to fidaxomicin in these patients and enhanced pharmacovigilance should be in place to monitor adverse events in this and other high risk populations." It is noted that a non-interventional study of the use of oral fidaxomicin in the clinical setting planned to be conducted in Europe and now to be extended to the US and Canada, has been proposed to further characterise the Important missing information: 'Patients with severe renal impairment', 'Patients with moderate to severe hepatic impairment', 'Patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis)' and 'Patients with life threatening or fulminant CDI, including pseudomembranous colitis'*. This was considered acceptable.

Consequently if this application is approved the following specific conditions of registration should be applied:

- The Australian Risk Management Plan Version: 1, dated 22 September 2012, including additional pharmacovigilance activities to monitor changes in antimicrobial resistance patterns in Australia and to further characterise the Important potential risk: '*Decreases in WBC, neutrophil and lymphocyte counts*' as agreed with the TGA, must be implemented.
- Post marketing reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Unless agreed separately between the supplier, who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter and subsequent reports must be submitted annually. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The annual submission may be made up of two periodic Safety Update Reports each covering six months.

For completeness advice on each specific recommendation follows:

TGA Recommendation 1

The sponsor has provided an assurance that any response to any safety considerations raised by the nonclinical and clinical evaluators will include due consideration of the relevance of these safety considerations for the AU RMP and duly include appropriate information in the AU RMP. This was considered acceptable.

TGA Recommendation 2

The sponsor has modified the AU RMP describing how the routine pharmacovigilance system in Australia is consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).* Novotech (Australia) Pty Ltd's correspondence of 1 November 2012 has also advised it has been contracted by the sponsor to be the pharmacovigilance service provider for the product in question and provided the details of the Australian pharmacovigilance contact person. This was considered acceptable.

TGA Recommendation 3

The sponsor has stated that currently there is no proposal to conduct in Australia any of the specified studies in the Pharmacovigilance Plan, including the postmarketing surveillance program to monitor changes in antimicrobial resistance patterns. However, this is inconsistent with the sponsor's response quoted in the CER dated 25 October 2012, which states: *"STA is evaluating the best method to conduct surveillance in Australia (i.e. either arrange for sentinel sites in Australia to submit toxin-positive stool samples/C. difficile isolates to an existing program, or alternatively initiate a new local program)."* Furthermore the clinical evaluator has recommended that the risk of development of resistance will require systematic surveillance. This was supported by ACSOM advice that the implementation of an Australian specific study to monitor changes in antimicrobial resistance patterns is important from a public health perspective. This remains an outstanding recommendation which the sponsor must address in an appropriate manner, preferably before this application is approved.

TGA Recommendation 4

The sponsor has modified Section 2.6 of the AU RMP to specify the known milestones for each of the planned clinical studies and provided an assurance that updates for each of these studies will be included in future PSURs. This was considered acceptable.

TGA Recommendation 5

The sponsor has modified Section 2.6 of the AU RMP to include planned reporting dates and known milestones for each of the planned clinical studies. This was considered acceptable.

TGA Recommendation 6

The sponsor has provided an assurance that any response to any safety considerations or conclusions made by the nonclinical and clinical evaluators will be duly addressed in the AU RMP. This was considered acceptable.

TGA Recommendations 7 and 10

The sponsor has modified Sections 3.1 and 5 of the AU RMP to include information for all the Important potential risks, not just for '*Development of microbial resistance to fidaxomicin*'. This information indicates that routine risk minimisation is included in the *Warnings* and *Precautions* sections of the Australian PI for all the Important potential risks. However for the majority of these Ongoing Safety Concerns no such information in the Australian PI can be found and therefore cannot be assessed. This can be dealt with administratively, preferably before this application is approved.

TGA Recommendation 8

The sponsor acknowledges the inconsistency between the information included in Sections 3.1 and 5 of the AU RMP for patients receiving repeated or extended fidaxomicin treatment courses when compared to the proposed Australian PI. The sponsor states that until such time as the clinical evaluation and nonclinical evaluation reports are available, the modified Sections 3.1 and 5 of the AU RMP has been modified to state '*CCDS and Australian Product Information **may state** lack of data availability and advise use of caution in this population*'. This is not entirely satisfactory. Nevertheless, this can be dealt with administratively, preferably before this application is approved.

TGA Recommendation 9

The sponsor has modified Section 3.2 of the AU RMP to include information on the potential risk with medication error with fidaxomicin. This was considered acceptable.

TGA Recommendation 11

In regard to the proposed routine risk minimisation activities, the sponsor has noted the recommendations made to the Delegate concerning revision to the draft product information document, but has made no material comment. Consequently these remain outstanding recommendations to the Delegate.

TGA Recommendation 12

In regard to the proposed routine risk minimisation activities, the sponsor has noted the recommendations made to the Delegate concerning revision to the consumer medicine information document but has made no material comment. Consequently this remains an outstanding recommendation to the Delegate.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The chemistry, manufacturing and controls aspects of the submission have been evaluated by TGA's Pharmaceutical and Chemistry Evaluation area. A number of questions were raised following the initial evaluation of this submission and the applicant has provided satisfactory responses to these questions. There are no outstanding issues in regards to the fermentation process and pathogen/prion safety. The revised PI submitted with the sponsor's consolidated response to TGA's questions is satisfactory in respect of chemical and pharmaceutical matters. The Provisional ARTG Records in Premier are considered accurate.

Study OPT-80-005 was discussed in quality evaluation. This study assessed the fidaxomicin bioavailability at fasted and fed (high fat meal) state following the administration of 2 x 200 mg of the proposed commercial formulation. The active metabolite, OP-1118, was also monitored. The result showed that for fidaxomicin and its metabolite, the extent of exposure (AUC_{0-t}), but not the peak exposure (C_{max}), was equivalent in the fed state compared to the fasted state, and consumption of a high-fat meal led to a slightly delayed T_{max} of 1 h and a 22% and 33% reduction in C_{max}, with respect to fidaxomicin and its metabolite, OP-1118. The applicant has stated that these differences in C_{max} are not considered to have clinical relevance, given that systemic exposure is not relevant to efficacy for *Clostridium difficile* infections, which are confined

to the gut. The evaluator commented that there is no mention of these results in the draft PI.

This submission has been discussed at the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) meeting. The PSC endorsed all the issues raised and supported the TGA questions on the limits for impurities in the drug substance and degradants in the drug product specifications. The PSC advised that the sponsor should be asked to provide batch analysis and stability data generated using drug substance manufactured at the two nominated drug substance manufacturing sites and to ensure that the drug substances from the two manufacturing sites are represented in the batch analysis and stability trials for the drug product. The PSC agreed that the attention of the Delegate and ACPM should be drawn to the lower availability of fidaxomicin metabolite from the formulation when administered under fed conditions. There are now no objections in respect of chemistry, manufacturing and controls to registration of fidaxomicin (Dificid) 200mg tablets with a shelf life of 3 years below 25°C. The evaluator raised a number of issues to the attention of the Delegate (see *Quality Findings* above).

The comments from Medicines Toxicology Evaluation Section regarding the impurities are provided below:

> *Twenty chemicals that required qualification were identified as impurities in the fidaxomicin drug substance or drug product. The proposed specification limits for all the impurities exceeded the ICH qualification threshold. Some of these impurities, including the major impurity OP-1405, were qualified through toxicological studies. All impurities were qualified genotoxicologically in an in vivo assay for liver and duodenal cell DNA damage. The limits of [information redacted] were adequately qualified for general toxicity.*
>
> *The levels of other impurities [information redacted] were too low to be detected in the submitted repeat dose toxicity study and are therefore not qualified from a toxicological point of view. Considering the low systemic absorption of fidaxomicin (the largest fraction is contained in the faeces), the short duration of the clinically proposed treatment and the potential severity of the condition, this may be acceptable on clinical grounds.*

The Delegate agreed with the comments made by Toxicology Evaluation Section in relation to the acceptability of these impurities in the context of low systemic absorption of fidaxomicin, the short duration of the proposed use and the severity of the disease condition.

Nonclinical

The nonclinical evaluator is of the view that the nonclinical dossier contained no major deficiencies. The following summary was provided in the non-clinical evaluation report:

- Fidaxomicin is a narrow spectrum antibiotic with bactericidal activity against *Clostridium difficile* with only moderate activity against other gram positive bacteria *in vitro*. Fidaxomicin effectively prevented lethal *Clostridium difficile* infection in clindamycin pretreated hamsters. Overall the nonclinical pharmacology studies supported the proposed dose and part of the proposed indication; *the treatment of Clostridium difficile infection*.
- Safety pharmacology studies revealed no clinically relevant hazards.
- Fidaxomicin was well tolerated in rats, dogs and monkeys.
- Fidaxomicin did not show genotoxic potential in animal studies. The lack of carcinogenicity studies is acceptable.

- Fidaxomicin did not show reproductive toxicity, pre- and post-natal studies were not conducted.
- Amendments to the draft Product Information were recommended.
- There are no major nonclinical objections to registration. However, not all of the specified impurities were toxicologically qualified. Considering the low systemic absorption of fidaxomicin (the largest fraction is contained in the faeces), the short duration of the clinically proposed treatment and the potential severity of the condition, this may be acceptable on clinical grounds.

Clinical

For pharmacokinetics assessment, one food-effect study, one single dose pharmacokinetics (PK) study, one multiple dose PK study and a number of drug-drug interaction studies were submitted. All these studies were conducted in healthy adult volunteers. For clinical efficacy and safety assessment, one Phase II dose-finding study and two Phase III pivotal studies were submitted. The three clinical studies were carried out in adult patients with CDI (*Clostridium difficile* infection).

A study to assess the absolute bioavailability of fidaxomicin has not been conducted. The justification for not conducting such a study is considered acceptable. The factors supporting this included local mode of action, localised pathology for which usage is being sought, well-characterised and simple metabolic fate.

Pharmacokinetic analyses

Food effect Study OPT-80-005

Study 005 assessed the relative bioavailability of oral fidaxomicin at fed and fasted state. The result of this study showed that the systemic exposure to fidaxomicin appears to be very small at "ng" range for both fidaxomicin and its metabolite, and administration with food does not increase the drug exposure. Absence of fidaxomicin in urine sample and high recovery (~75%) in faeces support any biotransformation limited mainly to the gastrointestinal tract. Based on these data, the clinical evaluator is of the view that it is acceptable to recommend fidaxomicin be taken regardless of food intake.

PK analyses from Phase I PK studies OPT-80 1A-SD and OPT-80 1B-MD

Study OPT-80 1B-SD was a Phase I single dose study assessing the PK of single, escalating doses of fidaxomicin (100 mg, 200 mg, 300 mg and 400 mg) in 16 healthy volunteers. Study OPT-80 1B-MD was a multiple dose study assessing the steady state fidaxomicin PK in 24 healthy volunteers who took 10 days of various daily doses of fidaxomicin (150 mg, 300 mg, and 450 mg). Overall, the systemic absorption of fidaxomicin is very limited with C_{max} at 5-10 ng/mL. The multiple dose study yielded much lower plasma concentrations compared to the single dose study and the sponsor commented that this could be due to the use of formulations that possess different absorption characteristics. The multiple dose PK study used powder filled capsules whereas a liquid filled capsule was used in the single dose study. Due to insufficient plasma data points above lower limit of quantification (LLOQ) for analysis and no PK parameters could be defined from the multiple dose PK study. In the single dose study, over 92% of the orally administered drug was accounted for in the faeces as fidaxomicin or its primary metabolite OP-1118 and less than 1% of the administered dose is excreted via renal route.

PK analysis from Phase III studies 003 and 004

The PK analyses from the two Phase III studies showed that the mean fidaxomicin concentration 3-5 h post-dose at both Day 1 and End of Treatment (EOT) were around 20

and 40 ng/mL. Plasma levels of the main metabolite OP-1118 were approximately 2 to 3 times that of the parent compound. The plasma concentrations of fidaxomicin and OP-1118 were mildly elevated in the elderly (> 65 years), though the levels were still in the ng/mL range. The plasma concentrations were mildly elevated in those with renal impairment (eCCL < 50 mL/min) compared to those with normal renal function (estimated creatinine clearance (eCCL) ≥ 50 mL/min). When faecal samples were available from clinical failures, the mean faecal levels and OPT-80/MIC ratios were similar between cures and failures. Overall, all post dose plasma measurements were in ng/mL range. There was no plasma accumulation from baseline to EOT. The average faecal drug levels were nearly 5,000 times higher than the 0.25 μg/mL MIC_{90} against *Clostridium difficile*.

The clinical evaluator is of the view that slightly higher values in the elderly and in patients with impaired renal function do not indicate clinically significantly higher systemic exposure compared to the overall results. There is indication that the overall systemic exposures obtained in this patient population were somewhat higher than those obtained in the healthy volunteers. However, the systemic exposure is very small and supports the conclusion that the drug principally acts locally with negligible systemic absorption.

Nonclinical in vitro PK data

Fidaxomicin is not metabolised by human CYP enzymes and does not induce or inhibit these enzymes *in vitro*. Its biotransformation involves hydrolysis of isobutyryl ester to form OP-1118 likely via an esterase, along with a small amount of glucuronidation and sulfation. *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. It is not clear if there are any unaccounted metabolites. However, considering fidaxomicin systemic absorption is very low and the usage is only for 10 days, the lack of characterisation of the human metabolism can be accepted.

PK interaction studies

The submitted PK drug interaction studies were discussed in the clinical evaluation report. Co-administration with a single dose of cyclosporine resulted in a 4.2 and 1.9 fold increases in fidaxomicin C_{max} and AUC and 9.5 and 4.1 fold increases in OP-1118 C_{max} and AUC. Half-life was not affected. The mechanism of the interaction seems to be increased absorption due to inhibition of transporter proteins, most likely P-gp, at intestinal level.

Co-administration of the P-gp substrate digoxin with fidaxomicin (200 mg twice daily) in healthy volunteers resulted in an increase in digoxin C_{max} of 14% and AUC of 12%.

The potential of fidaxomicin to alter the CYP mediated metabolism of S-warfarin, omeprazole and midazolam was assessed in a cocktail interaction study. S-warfarin, omeprazole and midazolam are probe substrates for CYP2C9, CYP2C19 and CYP3A4/5, respectively. The study results suggest that fidaxomicin has no clinically relevant effect on CYP2C9, CYP2C19 and CYP3A4.

The applicant is of the view that steady-state administration of 200 mg fidaxomicin did not significantly alter the drug metabolising capacity of CYP2C9, CYP2C19 and CYP3A4/5 to metabolise S-warfarin, omeprazole or midazolam respectively, and no dose changes are therefore proposed in the draft PI.

However, these interaction studies were only conducted in small number of subjects and it is difficult to draw conclusion regarding safety of increased exposure from these small studies. The Delegate agrees with the evaluator that a precautionary statement should be included in the PI in relation to these interactions and therapeutic drug monitoring of these drugs before and at the end of 10 day course with fidaxomicin in association with any of these drugs should be considered on individual basis.

Pharmacodynamics

Clinical and nonclinical evaluation report discussed the studies that provided the pharmacodynamics data. Fidaxomicin is a novel antibiotic agent and it acts via inhibition of RNA synthesis by bacterial RNA polymerase at a distinct site from that of the currently used RNA polymerase inhibitors. It has narrow spectrum of antibacterial activity. It is bactericidal against *C. difficile*. Gram negative organisms both aerobic and anaerobic are intrinsically insensitive. Fidaxomicin has variable activity against Gram positive anaerobic bacteria, facultative and aerobic Gram positive bacteria. It does not exhibit cross resistance to other classes of antibiotics. The risk of development of bacterial (*C. difficile*) resistance to fidaxomicin is considered low but a post-marketing surveillance program would be required to monitor the antimicrobial resistance patterns.

Efficacy and safety

Phase II dose finding study OPT-80-2A

Study OPT-80-2A was a Phase II dose finding study and it was an open-label, randomised, parallel groups study conducted in patients with mild to moderate *C. difficile* Infection. The participating patients were male or female, over 18 years of age who may have been hospitalised or treated in outpatient setting for mild to moderate CDI as defined by:

- Diarrhoea - change in bowel habits with 3 or more unformed bowel movements in 24 h, or more than 6 loose or watery stools within 36 h; and
- Presence of either Toxin A or B of *Clostridium difficile* toxin in stool.

Patients with a single recurrence episode of recurrent were allowed to enrol but those with multiple recurrences of CDI within the past 3 months were excluded. Patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) were also excluded. Up to 3 doses of metronidazole and/or vancomycin within 24 h were allowed where the investigator felt clinical imperative to start the treatment before availability of the results for stool toxin. Any other antibiotic or treatment of CDI was an exclusion criterion. Fidaxomicin was administered at 3 different doses (50 mg, 100 mg and 200 mg twice a day (bd) for 10 days). There was a dose response and clinical cure and relief of symptoms of CDI increased with increasing dose. A placebo comparator was not included but is considered appropriate due to the nature of the illness. The results support the use of fidaxomicin 200 mg bd for further clinical testing.

Pivotal studies 003 and 004

The two studies (Study 101.1.C.003 (Study 003) and Study 101.1.C.004 (Study 004)) have the same design feature, both are multi-centre, double-blind, randomised, parallel group studies that used non-inferiority design to compare the safety and efficacy of fidaxomicin (200 mg q12h) with vancomycin (125 mg q6h) for 10 days in patients with CDI. Study 003 only included sites from USA and Canada while Study 004 included study sites from Europe and North America. Inclusion and exclusion criteria were discussed in detail in the clinical evaluation report (CER).

The primary objectives of the two studies were to demonstrate that the cure rate of CDI following fidaxomicin treatment is non-inferior to that following vancomycin treatment and to assess the safety of fidaxomicin in subjects with CDI. The secondary objective was to evaluate the recurrence rate and global cure rates of CDI following treatment of fidaxomicin compared with vancomycin.

The primary efficacy endpoint was the primary cure rate in the PP population and modified ITT (mITT) populations. Secondary efficacy endpoints were the recurrence rate in the PP and mITT populations (Studies 003 and 004) and the global cure rate in the PP and mITT populations (Study 004). Explorative variables included global cure rate in the

PP and mITT populations (Study 003) and time-to-resolution of diarrhoea (TTRD) (Studies 003 and 004).

Clinical cure was defined as subjects who (in the view of the investigator) required no further CDI therapy 2 days after completion of study medication, and subjects who had 3 or fewer unformed stools for 2 consecutive days and remained well before the time of study medication discontinuation were considered cured. Subjects who were considered cured based on stabilisation and improvement in CDI signs and symptoms were evaluated 2 to 3 days after the end of therapy (EOT). If they remained stable and were not considered to require further CDI therapy to maintain their stable state, they were to be followed for recurrence as cures. Subjects who had rectal collection devices were considered to have resolution of diarrheal when the volume (over a 24 h period) was decreased by 75% compared with the volume observed at admission or when the subject was no longer passing liquid stools. Failure was defined as subjects who, in the opinion of the study investigator, required additional CDI therapy were considered failures. Global cure rate was defined as the number of subjects in each treatment group who had been evaluated as cured and who did not have a recurrence within 30 days after discontinuation of treatment. Time-to-resolution of diarrhoea (TTROD) was defined as the time elapsing (days and h) from start of treatment to resolution of diarrhoea.

The mITT Population for Cure was the group of subjects with CDI confirmed by positive toxin assay and who received at least 1 dose of study medication. The mITT Population for Recurrence was the group of subjects in the mITT Population for Cure who were classified as cured at the end of therapy.

The PP Population for Cure was the group of subjects included in the mITT population who met all inclusion criteria and no exclusion criteria, who required at least 3 complete days for failures and 8 complete days for cures, who had an EOT clinical evaluation, and did not have significant protocol violations. The PP Population for Recurrence was the group of subjects in the PP Population for Cure who were cured at EOT, and were followed for recurrence up to the post-study visit or experienced a recurrence ≤ 30 days post treatment and who did not use concomitant CDI therapy or other drugs which could have confounded the assessment of recurrence.

Study Subjects were randomised and stratified at each site on the basis of either having a single prior episode within 3 months or having no prior occurrence within the last 3 months. For Study 003, a total of 629 patients were enrolled with 623 receiving study drug (300 received fidaxomicin and 323 received vancomycin). A total of 54 patients (22 patients in the fidaxomicin group and 32 patients in the vancomycin group) withdrew from the study. For Study 004, a total of 535 patients were enrolled with 524 receiving study drug (260 on vancomycin and 264 on fidaxomicin). A total of 79 patients (45 patients in the fidaxomicin group and 34 patients in the vancomycin group) withdrew from the study. The treatment groups were generally comparable for demographic characteristics within each study. The median age was 63 years and 66 years in the two studies, respectively.

Efficacy analysis of study 003

Clinical cure rate

Based on mITT analysis, the proportion of patients achieved clinical cure at the end of 10 day treatment (EOT) was 88.2% in fidaxomicin group and 85.8% in vancomycin group. The difference was 2.4% (95% CI:-3.1% to 7.8%). A similar result was obtained in the PP population. The non-inferiority was thus demonstrated based on pre-defined criterion of a -10% margin. The cure rates for fidaxomicin were numerically higher but not statistically superior to vancomycin. A sensitivity analysis to assess the robustness of the primary result, using an alternative definition of cure, that is, ≤ 3 unformed bowel movements during treatment sustained to the EOT, supported the primary results.

Recurrence rate

The recurrence rate was examined based on follow-up for 28 (±2) days after the last dose of in patients who achieved cure at EOT. In mITT population, 15.4% patients in fidaxomicin group compared to 25.3% patients in vancomycin group experienced recurrence. The difference was -9.9% in favour of fidaxomicin (p = 0.005) with 95% CI of -16.6% to -2.9%. In the PP population, 13.3% patients in fidaxomicin group compared to 24.0% patients in vancomycin group experienced recurrence. The difference was -10.7% with 95%CI from -17.9% to -3.3% (p = 0.004). The median time to recurrence could not be calculated as recurrence rates were < 50% in both groups.

Global cure rate

The global cure rate was 74.6% in fidaxomicin group compared to 64.1% in vancomycin group in the mITT population. The difference was 10.5% with 95%CI from 3.1% to 17.7% (p = 0.006). The results were similar in PP population.

Median time to resolution of diarrhoea (TTROD)

In the mITT population, TTROD was 58 h (95%CI from 54 to 73 h) in fidaxomicin group compared with 78 h (95%CI from 60 to 95 h) in vancomycin group. The difference was not statistically significant. At baseline, the mean unformed bowel movements (UBMs) were 8.1 (± 4.2) and 8.4 (± 5.4) per day in fidaxomicin and vancomycin groups respectively. On study day 12, the mean UBMs per were 0.4 (± 1.3) and 0.7 (± 1.6) for fidaxomicin and vancomycin groups respectively.

Subgroup analyses

For the clinical cure rate, analysis based on a number of baseline features were carried out and indicated consistent effect across studied strata including the initial strain of *C. difficile* (BI/non-BI) and the 2 formulations used in the trial. The cure rates at most participating centres were similar in both study drugs. A number of subgroup analyses relating to recurrence rate were conducted and showed consistent effect across all studied strata. Notable instances where recurrence rates were higher in fidaxomicin-treated group n included Black participants, CDI antibiotic 24 h prior to study ≥ 4 doses, and initial BI strain. Recurrence rates by centres were generally similar. The subgroup analyses for global cure rates also showed consistent effect across all strata. As noted earlier for the recurrence rate, the global response rate with fidaxomicin treatment (57.3%) was lower compared to that with vancomycin treatment (63.9%) when the initial strain of *C. difficile* was BI.

Efficacy analysis of study 004

Clinical cure rate

Based on mITT analysis, the proportion of patients achieved clinical cure at EOT was 87.7% in fidaxomicin group and 86.8% in vancomycin group. The 95% CI for the difference was 0.9% (95%CI -4.9% - 6.7%). In the PP population, the clinical cure rate in fidaxomicin group was 91.7% compared to 90.6% in vancomycin group. The difference was 1.0% (95% CI -4.3% - 6.3%). The non-inferiority was demonstrated based on pre-defined criterion. A supplemental analysis using modified definition of clinical cure (≤ 3 unformed bowel movements during treatment sustained to the EOT visit) supported the primary analysis.

Recurrence rate

In the mITT population at 28 ± 2 days after EOT, the recurrence rate was 12.7% in fidaxomicin group and 26.9% in vancomycin group. The 95%CI for the difference was -14.2% in favour of fidaxomicin (95%CI -21.4%, -6.8%, p < 0.001). In the PP population, the recurrence rate was 12.8% in fidaxomicin group and 25.3%in vancomycin group. The 95%CI for the difference was -12.5% in favour of fidaxomicin (95%CI -20.3%, -4.4%,

p = 0.002). The median time to recurrence could not be calculated as recurrence rate was below 50% in both groups. The Wilcoxon test was statistically significant (p < 0.0001) in favour of fidaxomicin.

Global cure rate

The global cure rate was 76.6% in fidaxomicin group and 63.4% in vancomycin group in mITT population. The 95%CI for the difference was 13.2% in favour of fidaxomicin (95%CI of 5.2%-20.9%, p = 0.001). The results were similar in PP population.

Median time to resolution of diarrhoea (TTROD)

In the mITT population, the median TTROD was 50 h (95%CI 30 to 66 h) for patients in fidaxomicin group compared to 48 h (95%CI 31 to 63 h) for patients in vancomycin group. The difference was not statistically significant.

Subgroup analyses

The subgroup analyses for clinical cure rate, recurrence and global cure rate were generally consistent with the overall results including baseline BI/non-BI strain type as were results from individual centres. An exploratory logistic regression analysis was carried using both mITT and PP datasets to assess predictors of recurrence. In the mITT population, no prior CDI episode, lack of concomitant systemic antibacterial therapy, mild baseline severity and fidaxomicin treatment were the covariates significantly associated with lower risk of recurrence. In PP population, fidaxomicin treatment, no concomitant systemic antibacterial therapy, not receiving CDI antibiotic within 24 h prior to study, low baseline severity and no prior CDI episode were significantly related to lower recurrence risk.

Microbiological analysis

Based on available data from the Phase III studies, no correlation between faecal concentrations, MIC and treatment outcome could be demonstrated, the faecal concentration/MIC does not appear to be a predictive pharmacodynamic parameter. However due to limited number of faecal samples at EOT, especially in patients with failure and large variations between individuals, these data is not considered conclusive.

In summary, both Study 003 and 004 successfully demonstrated that fidaxomicin is non-inferior to oral vancomycin with respect to investigator assessed clinical cure after 10 days of treatment and fidaxomicin was superior to vancomycin with respect to sustained efficacy, that is, prevention of CDI recurrence within 4 weeks after a 10 day treatment. The two trials provide reliable confirmatory evidence of efficacy. The trial design, comparator (vancomycin), the doses, the duration, and the non-inferiority margin used in the trial are considered appropriate.

Safety analysis

The safety of fidaxomicin were evaluated in healthy subjects (n = 172) in the Phase I PK studies and interaction studies and most of this experience was single dose exposure. A total of 612 adult CDI patients including elderly (n=285) were exposed to fidaxomicin in the Phase II and Phase III studies for treatment up to 10 days.

In the two Phase III controlled trials conducted in CDI patients, a total of 564 patients were treated with fidaxomicin and 583 were treated with vancomycin. Adverse events (AEs) were reported in 68.3% and 65.5% patients in the two groups respectively. Notable AEs (incidence ≥ 2%) with frequency higher in fidaxomicin group compared to vancomycin group respectively were anaemia (2.5% versus 2.1%), vomiting (7.3%versus 6.3%), abdominal pain (5.9% versus 3.9%), constipation (4.4% versus 2.1%), hypokalemia (7.3% versus 6.5%), hyperkalemia (2.8% versus 1.7%), headache (6.6% versus 4.6%), dizziness (2.8% versus 2.1%) and dyspnoea (2.5% versus 2.2). AEs leading to study drug discontinuation were reported in 5.9% and 6.9% patients in fidaxomicin and vancomycin

groups respectively. SAEs were reported in 25.7% fidaxomicin treated patients compared to 23.2% vancomycin treated patients. Notable SAEs (≥ 2 patients) with higher occurrence in fidaxomicin group were anaemia (4 versus 2), leucopenia (4 versus 1), thrombocytopenia (3 versus 2), lymphopenia (3 versus 2), neutropenia (4 versus 0), cardiac failure (5 versus 3), myocardial infarction (4 versus 2), atrial fibrillation (4 versus 1), GI hemorrhage (4 versus 1), intestinal obstruction (4 versus 1), abdominal pain (4 versus 1), megacolon (3 versus 0), haemorrhagic diarrhoea (2 versus 0), colitis (2 versus 0), chest pain (2 versus 1), sepsis (7 versus 5), bacteraemia (2 versus 1), hip fracture (2 versus 1), blood uric acid increased (5 versus 1), lymphocyte count decreased (4 versus 1), liver function tests abnormal (2 versus 1), WBC count decreased (2 versus 0), neutrophil count decreased (2 versus 1), hyponatremia (6 versus 3), hyperkalemia (5 versus 2), hypophosphatemia (5 versus 0), hypoglycaemia (3 versus 0), acute renal failure (4 versus 3), respiratory distress (3 versus 0), hypoxia (2 versus 1), chronic obstructive pulmonary disease (2 versus 0) and hypotension (2 versus 1). Gastrointestinal treatment-emergent AEs were reported in 31.4% in fidaxomicin group and 29.0% in vancomycin group. Identified GI bleeding Treatment-Emergent AEs were reported in 4.1% fidaxomicin treated patients compared to 3.1% vancomycin treated patients. AEs leading to death were reported in 36/564 (6.4%) fidaxomicin treated patients compared to 38/583 (6.5%) vancomycin treated patients. Shifts in WBCs were more prevalent in fidaxomicin group (4.1%) compared to vancomycin group (1.9%). The incidence of increased alanine aminotransferase was 1.6% in fidaxomicin group compared to 1.0% in vancomycin group.

The evaluator acknowledges the limitation with the safety assessment as the underlying disease may confound the safety profile of the trial drugs and placebo controlled data is not available. Despite the limitations, the evaluator was of the view that due to the controlled nature of the data that the overall AE profile of oral fidaxomicin is similar to oral vancomycin in the treatment of CDI including deaths and SAEs although the pattern for SAEs is somewhat different in the two groups. For fidaxomicin, the haematological effects especially on white blood cells and effects on hepatic function (enzymes) will need further collection of the data for convincing attribution.

Risk management plan

The RMP evaluator pointed out that a number of issues have not been satisfactorily addressed by the sponsor. The outstanding issues are listed below:

- Plan for postmarketing surveillance program in Australia to monitor changes in antimicrobial resistance patterns.
- Inclusion in the Australian PI all the Important potential risks, including the potential risk of neutropenia.
- Include in the Australian PI all the Important missing information (information in patients receiving repeated or extended fidaxomicin treatment, patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis); in patients with life threatening or fulminant CDI, including pseudomembranous colitis, in patients with severe renal impairment and patients with moderate to severe hepatic impairment, and information relating co-administration with potent inhibitors of potent P-glycoprotein inhibitors.

The ACSOM endorsed the need for Australian specific postmarketing drug resistance surveillance program. The additional advice from ACSOM includes that the enhanced pharmacovigilance should be undertaken for the high risk subpopulations that were omitted from the clinical studies, for example, it was considered likely that fidaxomicin will be used in patients with inflammatory bowel disease (IBD); even though patients with IBD were not included in the efficacy studies, and there is potential that the intestinal

barrier will be more permeable to fidaxomicin in these patients and enhanced pharmacovigilance should be in place to monitor adverse events in this and other high risk populations.

Based on the RMP evaluation, the RMP evaluator recommends that the conditions of registration should include the Australian Risk Management Plan Version 1 dated 22 September 2012 and post marketing reports be submitted at specified intervals.

Risk-benefit analysis

Delegate considerations

Pharmacokinetics/pharmacodynamics

Fidaxomicin appears to have a simple pharmacokinetics and is not absorbed systemically to any clinically significant degree. The excretion is via faecal route as intact parent drug and its metabolite. There is small food effect (lower bioavailability) which is not considered clinically relevant. The effect on cyclosporine, digoxin and warfarin may be clinically important and such co-administration should be monitored including measurement of plasma drug levels for these drugs.

Fidaxomicin has a narrow spectrum of antimicrobial activity with a long post antibiotic effect and it lacks cross resistance to other antibiotic with a possible low risk of resistance development. Fidaxomicin achieves very high faecal levels; many thousands of times it MIC_{90} value against *C. difficile*. However, a relationship between faecal levels, MIC and clinical failures was not established in the clinical efficacy trials.

It is not known to what extent the systemic exposure might increase in case of severe degree of inflammatory bowel in CDI patients. Based on very variable data and a between study comparison, the C_{max} of fidaxomicin and OP-1118 in CDI patients was higher than the C_{max} values measured in healthy volunteers. This increased absorption in CDI patients is likely due to the inflammatory state of the bowels resulting from the infection.

Efficacy

The efficacy of fidaxomicin was based on the two pivotal efficacy studies. The two studies were similarly designed, active (oral vancomycin) controlled, randomised, double blind studies conducted in adult patients with CDI. The two studies successfully established non-inferiority of 10 day course of oral fidaxomicin (200 mg every 12 h) to oral vancomycin (150 mg oral every 4 h) with respect to clinical cure. The studies were well planned and the non-inferiority was tested using both modified ITT and PP populations and the lower side 95% CI for the treatment difference were within the predefined non-inferiority margin. Fidaxomicin treatment was shown to have led to lower rate of recurrence within 28 days of completing treatment compared to vancomycin (15% versus 25% and 13% versus 27%). However, the evaluator is of the view that this is more appropriate a measure of sustained efficacy or alternatively more appropriate timepoint for measurement of clinical cure rather than prevention of recurrence. Based on these findings, the evaluator agreed that a first line indication is appropriate; however, the evaluator did not support the sponsor's proposed indication which includes '*reducing the risk of recurrence when used for treatment of CDI*'. The Delegate agrees with this view and also notes that reducing the risk of recurrence is not included in the FDA and European Medicines Agency (EMA) approved indications for fidaxomicin. The submitted studies were not prospectively designed to prove prevention of re-infection with a new strain.

Safety

The dataset for safety evaluation is considered too small to enable full safety characterisation of a new chemical entity. Based on the submitted data, the adverse effects

profile of fidaxomicin was similar to vancomycin. Although absorption may be considered relatively low, it cannot be ruled out that levels of systemic exposure may lead to potential safety effects, especially in patients with damaged intestinal mucosa, such as patients with severe CDI and patients with inflammatory intestinal diseases. The safety data are currently missing in patients who require repeated use of fidaxomicin. The potential emergence of resistance in the clinical setting is not known. The events of neutropenia, increased transaminases and gastrointestinal haemorrhage occurred more commonly in the fidaxomicin group, although confounding factors may partly contribute to the higher incidence of these events. Due to the limited clinical experience for this new drug, monitoring of adverse events concerning laboratory parameters including haematological and hepatic data should be performed with cumulative reporting in future PSURs.

Benefits and risks balance

Vancomycin is the currently only approved antibiotic for use in the treatment of *Clostridium difficile* infection, although a number of other antibiotics such as metronidazole are used off label in clinical practice. Oral vancomycin acts locally whereas metronidazole is absorbed systemically. The expected benefits with oral fidaxomicin are comparable to that with vancomycin in terms of clinical response at end of the therapy. Fidaxomicin treatment showed superior sustained efficacy compared to vancomycin in terms of recurrence at 4 weeks after completion of treatment. Potential risks are identified for some adverse events, such as neutropenia, increased transaminases, gastrointestinal haemorrhage and so on and further monitoring of these adverse events in the postmarketing period is required. Drug-drug interactions assessed during drug development indicate small magnitude of changes in pharmacokinetic when fidaxomicin was used with P-gp or CYP substrates. However, these may be meaningful in clinical practice and for narrow therapeutic index drugs such as cyclosporine, digoxin and warfarin, concomitant use with fidaxomicin may need monitoring. The risk of resistance development is low but non-negligible and will require systematic surveillance in the postmarketing period. Overall, the risk-benefit balance is in favour of benefit especially in light of sustained efficacy at 4 weeks compared to vancomycin and the postulated low potential for cross-resistance.

Product Information

Product Information (PI) has been reviewed by the evaluators from Pharmaceutical and Chemistry, Nonclinical, Clinical and RMP evaluation areas. A draft PI incorporating recommended changes should be submitted by the sponsor with their Pre-ACPM response. Further changes to the PI may be required after the ACPM discussion.

Specific issues for ACPM advice

The advice from ACPM was requested, specifically with the following aspects:

1. The evaluator agrees that fidaxomicin treatment was shown to have led to lower rate of recurrence within 28 days of completing treatment compared to vancomycin (15% versus 25% and 13% versus 27%) and this is the important benefit of fidaxomicin over vancomycin. However, this is more appropriate a measure of sustained efficacy rather than prevention of recurrence. Does ACPM agree that the following statement should not be included in the indication?

   "Reducing the risk of recurrence when used for treatment of CDI"

2. The risk of development of resistance is considered to be low, what is the view of the ACPM in terms of the requirement of Australian specific surveillance program to monitor the changes in antimicrobial resistance patterns?

3. What is the ACPM's view in relation to the overall balance of benefits versus risks of fidaxomicin administration for the treatment of *Clostridium difficile* infection in adults?

Proposed action

Pending the advice from the ACPM, the Delegate proposed the registration approval of fidaxomicin (200 mg) tablets for the following indications:

> *Fidaxomicin is indicated for the treatment of Clostridium difficile infection in adults.*
>
> *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 diagnosed to be caused by Clostridium difficile.*

The recommended dose is 200 mg administered twice daily for 10 days. Dificid can be taken before, during or after meals. The finalisation of this application is subject to satisfactory negotiation of the PI and clearance of the GMP.

The conditions of registration include:

- Implementing the Australian Risk Management Plan (RMP) version 1 dated 22 September 2012 and subsequent updates to the RMP.
- Providing post marketing reports (PSURs) at the intervals specified by the Office of Product Review (OPR), TGA.

Response from sponsor

Proposed indication

The therapeutic indication sought has been amended in the Product Information (attachment C1), in response to the Delegate's request as follows:

> *Fidaxomicin is indicated for the treatment of Clostridium difficile infection (CDI) in adults.*
>
> *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 diagnosed to be caused by Clostridium difficile.*

Although the Delegate is requesting agreement from ACPM that the statement *'Reducing the risk of recurrence when used for treatment of CDI*' should not be included in the indication, the sponsor proposed the following alternative language in this section of the PI:

> *Dificid has been shown to be effective in sustaining CDI clinical response for 28 days in controlled clinical trials [See CLINICAL TRIALS].*

The sponsor was open to alternative language as the sponsor fundamentally believes that it is both appropriate and vital that this information be captured in this section based on the following:

Results for both sustained clinical response and recurrence from the two pivotal Phase III studies were both statistically and clinically robust as well as highly clinically relevant.

- Both "sustained clinical response" (previously known as "global cure") and "recurrence" were pre-specified as either secondary or exploratory endpoints in the statistical analysis plans for the 003 and 004 pivotal Phase III studies and as such, are statistically legitimate.

- Superiority analyses for both endpoints were also pre-specified in the respective statistical analysis plans; these analyses were not post-hoc.
- Clear and consistent superiority on both endpoints was shown across both clinical studies with the separation between treatments being highly clinically significant.
- There is a strong microbiological basis for the superiority of DIFICID over available therapies (for example, maintenance of the normal intestinal microflora), and it is in fact these very endpoints where these findings manifest clinically.
- Key Opinion Leaders have advised that these results are highly clinically relevant with, for example, an overall 47% reduction in recurrence rate observed in DIFICID-treated patients versus vancomycin.

In summary, the sponsor stated that the proposed statement is a factual statement that is supported by valid, strong and consistent evidence from the two large-scale pivotal studies and is deemed clinically important by clinical experts. The clinical and statistical significance of the effectiveness of Dificid on recurrence rate and sustained clinical response are indisputable according to the sponsor.

Supporting data

Pharmaceutical chemistry evaluation

The relevant GMP clearance has been renewed and is current to 18 January 2015.

Nonclinical evaluation

The comments on the PI made by the nonclinical evaluator have been addressed.

Clinical evaluation

The clinical evaluator's comments on the PI have been addressed.

Risk Management Plan (RMP)

The RMP evaluation report listed the following outstanding issues that have not been satisfactorily addressed by the sponsor. Please find responses to each of these below:

Plan for postmarketing surveillance program in Australia to monitor changes in antimicrobial resistance patterns.

At this time, the sponsor is recommending no additional surveillance to be conducted in Australia for two primary reasons.

First, there are multiple surveillance studies ongoing or planned in diverse regions of the world, including ongoing studies in the USA and Europe, along with a study planned to initiate in Canada. It has been assumed, based on the rapid international emergence of the epidemic ribotype 027 strain, that spread of CDI strains occurred on a global scale. This was confirmed by a very recent publication[24], which used full-genome sequencing and phylogenetic analysis to confirm that these strains, which have arisen from two distinct lineages, have undergone global spread from North America (where both initially arose) to Europe, Asia and Australia. It is unlikely, therefore, that a problematic strain would be missed in a global surveillance program.

Second, as the likelihood of resistance development increases with the number of cases treated, it follows that surveillance has greater potential to pick up shifts in susceptibility in regions with a high prevalence of CDI, where a greater number of strains are exposed and a higher number of isolates can be monitored. A study in Australia, with its relatively small population and moderate incidence of CDI as compared with other regions

[24] He M et al, "Emergence and Global Spread of Epidemic Healthcare-Associated Clostridium difficile." Nature Genetics (2013) 45:109-113.

(estimated at 18-35.8 cases per 100,000 population[25], as compared to, for example, the USA, with over 100 cases per 100,000 population[26] may provide poor sensitivity for picking up shifts in susceptibility, whereas larger population centers and regions with high incidence of CDI, with their correspondingly higher use of fidaxomicin, may act as better "sentinel" regions by which shifts in susceptibility can be detected.

Although the sponsor does not plan surveillance immediately in Australia, the sponsor will remain alert for reports of lack of efficacy, which could indicate a loss of susceptibility, as part of our risk management plan.

The sponsor will also ensure continued evaluation of all available worldwide study data to periodically assess the need for a local (Australian) surveillance program.

Inclusion in the Australian PI all the important potential risks, including the potential risk of neutropenia.

All the important potential risks are subject to routine and enhanced pharmacovigilance activities, as specified in the Australian RMP. Please also refer to the latest PSUR for relevant detailed information on each of the potential risks (including neutropenia). As stated above, relevant wording on hypersensitivity has been added to the product information, based on post-marketing safety data. At present, there is insufficient data to include any additional information on these potential risks in the product information.

Inclusion in the Australian PI of all the important missing information:

1. *Patients receiving repeated or extended fidaxomicin treatment.*

As detailed in the AU RMP, information collected from this population is subject to routine pharmacovigilance activities in order to assess the safety and susceptibility of fidaxomicin in this setting. There are also ongoing postmarketing surveillance activities in the EU and ongoing clinical trials that may generate additional data.

From the last PSUR period, there had been 26 reports of extended treatment duration, including 15 case reports from the literature. Twelve of the literature reports were not associated with ADRs. The average duration of extended use was 16.5 days, ranging from 12-24 days. One patient reported in the literature died two months after fidaxomicin use from an underlying malignancy and there was one case of leucopenia. There was no adverse event identified as a result of the extended use. At present, it is not considered necessary to add a statement to the Australian PI, however all future data will be assessed and the PI amended as necessary.

2. *Patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis) and patients with life-threatening or fulminant CDI.*

The precaution statements in the Australian PI have been amended as suggested by the RMP evaluator to be in line with the precaution statements in the currently approved SmPC.

3. *Patients with severe renal impairment and patients with moderate to severe hepatic impairment.*

There are already adequate statements in the precautions section of the PI.

4. *Information relating co-administration with potent inhibitors of P-glycoprotein inhibitors.*

[25]Ferguson JK et al. "Clostridium difficile laboratory testing in Australia and New Zealand: national survey results and Australasian Society for Infectious Diseases recommendations for best practice." Pathology (2011) 43: 482–487

[26]Lucado J et al, "Clostridium difficile Infections (CDI) in Hospital Stays, 2009" HCUP statistical brief #124, 2012. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.jsp

As stated above, a precautionary statement was added to the PI, advising caution when fidaxomicin is co-administered with potent inhibitors of P-gp. The sponsor would also like to reaffirm at this stage that routine and enhanced pharmacovigilance activities are already being conducted in the 'high risk' populations, as requested by the RMP evaluator. These populations are specified in the RMP, and periodic updates on the available information on these populations are given in the PSURs.

Other comments:

'Suggestions about the Product Information (PI) Document (Delegate's Overview): Suggestion 5: The 'Adverse Reactions' sections of the PI should be updated to include all serious adverse reactions that are listed in the PSUR or in the tabulation of serious unexpected adverse reactions supplied with the pre-ACPM response'.

Serious unexpected adverse reactions are being monitored through routine pro-active global pharmacovigilance activities, which include updates to the product information, where appropriate.

From routine review of all serious unlisted events, it is considered not appropriate to include all of the serious unexpected events listed in these tabulations as adverse reactions in the PI. These events are mostly consistent with the underlying CDI, co-morbid medical conditions associated with CDI, or with other concurrent medical conditions of the patient, and do not raise new safety signals regarding fidaxomicin use. The sponsor also referred to the PSURs where serious unexpected adverse reactions are routinely assessed and discussed.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the modified indication;

For the treatment of confirmed Clostridium difficile (CDI) infections in adults

In making this recommendation the ACPM strongly supported the overall principle that ongoing surveillance and reporting of the occurrence and rate of resistance. This includes maintenance of PI/CMI currency on resistance. Such surveillance and reporting should be a routine responsibility for all sponsors of antibiotics. The ACPM also advised that the reports of neutropenia warranted a precautionary listing, given the small size of the population studied.

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI).

- a statement in the *Precautions / Contraindications / Clinical Trials / Dosage and Administration* sections of the PI and relevant sections of the CMI to more accurately reflect the levels of product impurity and the potential impact, particularly in the context of repeat dosing where there are a lack of data.[27]

[27] Based on further TGA review of the impurity issue, the Delegate considered it was justified not to include a statement regarding unqualified impurities in the Dificid PI and CMI at this stage. The TGA will consider further regulatory actions if there is any safety signal emerging in the future post-marketing phase.

- a listing in the *Precautions* section *of* neutropenia as a possible adverse event.[28]
- inclusion of current resistance status data.[29]

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Dificid tablet containing fidaxomicin 200 mg for oral administration, indicated for:

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

Specific conditions of registration applying to these therapeutic goods

The implementation in Australia of the fidaxomicin Risk Management Plan (RMP) version 1.3, dated 26 March 2013, included with submission PM-2011-04269-3-2, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

[28] Following further review, the Delegate considered that it was not considered necessary to include "neutropenia" in the Precautions section of the PI at this stage. However, "neutropenia" must be included in the Adverse Effects section of the PI and included in the RMP as "Important potential risks".
[29] Upon the advice from the ACPM, the sponsor agreed to conduct a microbiological surveillance program of clinical C. difficile strains, with isolates from multiple centres in Australia, to determine if changes in susceptibility patterns occur after fidaxomicin becomes available. The PI and/or CMI will be kept up to date with appropriate resistance data, as and when required.

Therapeutic Goods Administration

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