Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for rifaximin

Proprietary Product Name: Xifaxan

Sponsor: Norgine Pty Ltd

October 2015

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 <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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.

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List of abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ASA	Australian Specific Annex
AUC	area under the plasma concentration-time curve
AUClast	area under the plasma concentration-time curve from time zero to the time of the last measurement
AUCt1-t2	area under the plasma concentration-time curve from t1 to t2
bid	twice (two times) a day (*bis in die*)
Cmax	maximum plasma drug concentration
CMI	Consumer Medicine Information
E. coli	*Escherichia coli*
EAEC	enteroaggregative *Escherichia coli*
ETEC	enterotoxigenic *Escherichia coli*
FDA	US Food and Drug Administration
GI	gastrointestinal
GMP	Good Manufacturing Practice
ITT	intention to treat
MHRA	Medicines and Healthcare products Regulatory
MIC	minimal inhibitory concentration
MIC_{50}	minimal inhibitory concentration that inhibits 50% of bacterial isolates
MIC_{90}	minimal inhibitory concentration that inhibits 90% of bacterial isolates
PI	Product Information
qid	four times a day (*quater in die*)
RMP	Risk Management Plan

Abbreviation	Meaning
SAE	serious adverse event
SMX	sulphamethoxazole
tid	thrice (three times) a day
Tmax	time taken to reach the maximum plasma drug concentration
TMP	trimethoprim
TLUS	time to last unformed stool

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	21 May 2015
Active ingredient(s):	Rifaximin
Product name(s):	Xifaxan
Sponsor's name and address:	Norgine Pty Ltd 3/14 Rodborough Road Frenchs Forest NSW 2086
Dose form(s):	Tablet
Strength(s):	200 mg
Container(s):	Blister packs
Pack size(s):	9 tablets
Approved therapeutic use:	Xifaxan is indicated for the treatment of patients (≥ 12 years of age) with travellers' diarrhoea caused by non-invasive strains of *Escherichia coli* (see 'PRECAUTIONS', and 'CLINICAL TRIALS'). Travellers' diarrhoea describes a clinical picture predominantly observed in subjects travelling from developed to developing countries. It is most frequently caused by enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E. coli* (EAEC) and other non-invasive pathogens.
Route(s) of administration:	Oral
Dosage:	200 mg tablet taken orally three times a day for 3 days, with or without food
ARTG number (s):	222643

Product background

This AusPAR describes the application by Norgine Pty Ltd to extend the indications for rifaximin (trade name: Xifaxan). The rifaximin 550 mg tablet (AUSR R 183411) was approved in Australia in 2011 for the prevention of recurrence of hepatic encephalopathy. The sponsor is seeking to now register rifaximin 200 mg tablets for the indication:

> *Treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria.*

Rifaximin is a non-aminoglycoside, semi synthetic, non-systemic antibiotic derived from rifamycin. Rifaximin acts by binding to the β subunit of bacterial DNA dependent RNA

polymerase, resulting in inhibition of bacterial RNA synthesis. Other rifamycin antibiotics include rifampicin and rifabutin.

According to the sponsor, rifaximin has a broad antimicrobial spectrum against most of the gram positive and gram negative, aerobic and anaerobic bacteria responsible for intestinal infections. Due to very low absorption from the gastrointestinal (GI) tract, rifaximin is locally acting in the intestinal lumen and is not clinically effective against invasive pathogens, although these bacteria are susceptible to rifaximin *in vitro*.

Current guidelines recommend a single large dose of azithromycin or norfloxacin as first-line treatment for travellers' diarrhoea, with emerging quinolone resistance in gram negative pathogens, particularly in South Asia, to be taken into account when choosing appropriate therapy.

The sponsor states that:

> *The chemical development programme of rifaximin began in the early 1980s, when the originator company (Alfa Wassermann SpA) was looking for a non-absorbable derivative of rifamycin with the same broad spectrum activity as rifampicin to develop in the treatment of GI disease due to external bacteria (infective diarrhoea) or resident bacteria (such as hepatic encephalopathy).*

Rifaximin was initially registered internationally in 1985.

Rifaximin is also used 'off label' for conditions including *Clostridium difficile* (*C. difficile*) associated diarrhoea[1] and irritable bowel syndrome.[2]

The currently approved dosage regimen for the prevention of recurrence of hepatic encephalopathy is one Xifaxan 550 mg tablet taken orally twice a day, with or without food. The proposed dose for the new indication of treatment of travellers' diarrhoea is one Xifaxan 200 mg tablet taken orally three times a day for 3 days, with or without food.

Regulatory status

The regulatory status of Xifaxan 200 mg tablets for the treatment of travellers' diarrhoea at the time of this submission is shown in Table 1. Applications in European Union (EU) countries were submitted using the National procedure.

[1] Johnson S, et al. (2007) Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis.* 44: 846-8.
[2] Pimentel M, et al. (2011) Effects of rifaximin treatment and retreatment in nonconstipated IBS subjects. *Dig Dis Sci.* 56: 2067-72.

Table 1: Regulatory status of Xifaxan 200 mg tablets for the treatment of travellers' diarrhoea.

Country	Submitted	Approved	Comment	Indication
United States	21/12/2001	26/5/2004		XIFAXAN 200 mg tablets are indicated for the treatment of patients (> 12 years of age) with travellers' diarrhoea caused by non-invasive strains of Escherichia coli.
Belgium	TBA	Withdrawn 20/9/2011	Company withdrawal due to agency request for additional clinical data/studies	
Denmark	TBA	14/4/2010		Rifaximin is a non-absorbed antimicrobial agent belonging to the rifamycin group. It is indicated for the treatment of adult patients with traveller's diarrhoea caused by non-invasive enteric pathogens. Traveller's diarrhoea describes a clinical picture predominantly observed in subjects travelling from developed to developing countries. It is most frequently caused by enterotoxigenic Escherichia coli (ETEC), enteroaggregative E. coli (EAEC) and other non-invasive pathogens.
France	TBA	Withdrawn 09/4/2010	Company withdrawal due to agency request for additional clinical data/studies	
Germany	TBA	15/1/2008		Treatment of traveller's diarrhoea caused by non-invasive enteropathogenic bacteria in adults. Traveller's diarrhoea in terms of this indication is diarrhoea contracted when travelling to the Mediterranean, sub-tropical or tropical regions.
Sweden	TBA	Withdrawn 22/2/2012	Company withdrawal due to agency request for additional clinical data/studies	
Switzerland	TBA	Withdrawn 27/2/2009	Company withdrawal due to agency request for additional clinical data/studies	
United Kingdom	2007	2/12/2010		Rifaximin is indicated for the treatment of traveller's diarrhoea that is not associated with any of: Fever - Bloody diarrhoea - Eight or more unformed stools in the previous 24 h - Occult blood or leucocytes in the stool. Rifaximin may shorten the duration of diarrhoea when this is associated with non-invasive strains of E.coli

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <www.tga.gov.au/product-information-pi>.

II. Quality findings

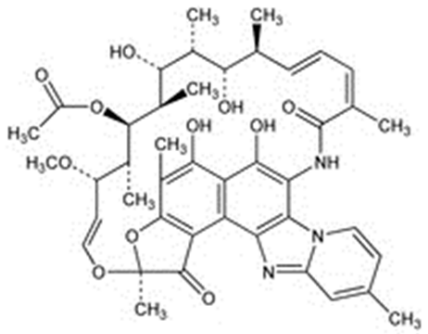
Introduction

Norgine has submitted an application to register rifaximin 200 mg film coated tablets under the trade name 'Xifaxan' as an additional strength with a new indication.

Drug substance (active ingredient)

Rifaximin is a semisynthetic antibiotic derived from the fermentation product rifamycin-B. It has very poor oral absorption and achieves high concentrations in the gut lumen following oral administration. The structure of the drug substance is depicted in Figure 1.

Figure 1: Chemical structure of rifaximin.



Rifaximin contains nine asymmetric carbons; the fermentation process fixes the stereochemistry at all nine asymmetric carbons, and no epimerisation occurs during subsequent synthetic transformations. *Cis/trans* isomerism is possible about each of the three double bonds in the molecule. Again, the fermentation process fixes the configuration at each of these sites.

Five crystalline polymorphic forms of rifaximin (α, β, γ, δ and ε) have been isolated and identified by X ray powder diffraction. However, only rifaximin α is obtained from the manufacturing procedure. This is critical as forms γ and δ exhibit significant systemic absorption.

Assurances were provided that the synthetic route, manufacturing processes and quality controls applied to the drug substance for use in the proposed 200 mg presentation are the same as those applied to drug substance used in the registered 550 mg presentation.

Drug product

The drug product is a film-coated tablet for oral administration, containing 200 mg of rifaximin, packaged in heat sealed PVC/PE/PVDC/Al blister packs. The tablets are manufactured by a conventional dry granulation process.

The proposed finished product specifications adequately control identity, potency and other physical, chemical and microbiological properties relevant to the clinical use of the product.

Satisfactory data was provided to support a shelf life of 3 years when stored below 25°C.

Biopharmaceutics

Rifaximin is not intended to be absorbed systemically. It is intended to exert its effect locally in the GI tract. The PI notes that systemic exposure of rifaximin following oral administration is extremely low regardless of dose, disease state, or feeding state.

Two comparative bioavailability studies were presented:

- Study RFPK9901: The Effect of Food on the Bioavailability of a Single Oral 400 mg Dose of Rifaximin in Healthy Volunteers
- Study CD0005.03: The Effect of Commercial Scale-up Manufacturing on the Bioavailability of a Single (2 x 200 mg) Oral Dose of Rifaximin, 200 mg Tablets, in Healthy Volunteers

Study RFPK9901

Administration of a single 400 mg oral dose to fasted and fed healthy subjects resulted in mean AUC values of 18.3 ng.h/mL and 34.7 ng.h/mL, respectively. Mean percent change for Cmax, Tmax, and AUClast was 286 ± 183%, 157 ± 85.4%, and 273 ± 212%, respectively (high fat breakfast relative to fasting).

Study CD0005.03

The study compared Tablet A, the proposed commercial formulation manufactured at commercial scale, with Tablet B, the proposed commercial formulation manufactured at pilot scale and used in several clinical trials. Cmax and AUC point estimates and confidence intervals are summarised in Table 2.

Table 2: Cmax and AUC point estimates and confidence intervals.

Parameter	Ratio (B/A)	90% CI
AUC_{last}	380.8%	183.6%, 790.1%
AUC	218.0%	127.6%, 372.4%
C_{max}	230.3%	160.6%, 330.2%

Quality summary and conclusions

There are no objections on chemistry and quality control grounds to the registration of the proposed 200 mg rifaximin tablets.

III. Nonclinical findings

Introduction

The nonclinical dossier comprised data previously submitted and evaluated in the sponsor's original application to register rifaximin for the prevention of recurrence of hepatic encephalopathy and a new repeat-dose dog toxicity study. Only the new study is reviewed in this evaluation report.

Pharmacology

The proposed indication is supported by previously evaluated nonclinical pharmacology studies. *In vitro* studies demonstrated high activity of rifaximin against a range of anaerobic bacteria of the faecal flora, as well as against enteropathogens causing travellers' diarrhoea. The development of resistance was no greater than that observed with related antibiotics, such as rifampicin. *In vivo* in rats, rifaximin inhibited most aerobic species and total anaerobic cocci at dose levels below the clinical dose.

Toxicology

It was difficult to achieve high plasma exposure ratios in animal studies with rifaximin-α because of the lack of absorption of the polymorph form. In the new 6 month study in dogs, a different form of rifaximin (100 and 1000 mg/kg/day) was used, in addition to rifaximin-α (1000 mg/kg/day). High systemic exposures were achieved in dogs dosed with the different form of rifaximin. The mean AUC values at 1000 mg/kg/day of the different form of rifaximin were 70-85 fold higher than the AUC in dogs dosed with 1000 mg/kg/day rifaximin-α (Table 3). The low dose of different form rifaximin (100 mg/kg/day) also resulted in systemic exposures higher than the exposure from 1000 mg/kg/day rifaximin-α. The systemic exposures in the 6-month dog study are compared with clinical exposures in Table 3.

Table 3: Comparison of systemic exposures in the 6 month dog study with human exposures.

	Dose (mg/kg/day)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Exposure ratio[a] 550 mg *bid*	Exposure ratio[b] 550 mg *bid* (hepatically impaired patients)	Exposure ratio[c] 200 mg *tid*
Male dogs	1000 alpha	136	5.5	0.5	6.5
	100 different form	995	40	3.8	48
	1000 different form	9760	397	38	467
Female dogs	1000 alpha	284	12	1.1	14
	100 different form	870	35	3.4	42
	1000 different form	24300	988	93	1163

a. Animal/human exposure ratio based on human AUC0-24h value of 24.6 ng.h/mL (AUCtau 12.3 ng·h/mL x 2) at 550 mg bid in healthy volunteers (RPFK 1007). b. Based on human AUC0-24h 260 ng·h/mL (AUCtau 130 ng·h/mL x 2) in hepatically impaired patients at 550 mg bid (RFHE 3002PK). c. Based on AUC0-24h 20.9 ng·h/mL (AUC0-8h at 200 mg/day 6.95 ng·h/mL x 3) in healthy volunteers with Shigella flexneri-induced diarrhoea (PK0303).

Involution of the thymus occurred in males in the new six month study at all dose levels, associated with a slight decrease in thymus weight, consistent with the previously evaluated 9 month dog study. This finding is common to all broad spectrum non absorbable antibiotics at high dose levels.[3]

A statistically significant decrease in white blood cells and lymphocytes in males and decreased red blood cells and haematocrit in females, which was not observed with rifaximin-α in this study or previously evaluated studies, were observed in the different form rifaximin group at 1000 mg/kg/day. Decreased lymphocyte counts were also seen in the low dose different form rifaximin male group (100 mg/kg/day), but not in female groups even at the high dose (1000 mg/kg/day) with higher AUC values than in males. A small decrease in white blood cell counts in the rifaximin-α male group (4% compared to the control group) achieved statistical significance, but there was no similar change in the female group or in previously evaluated studies with rifaximin-α.

In females dosed with different form rifaximin at 1000 mg/kg/day (not at 100 mg/kg/day), there was an increase in interstitial inflammation of the kidneys and minimal mineralisation of the ovaries.

The new findings (decreased white and red blood cell and lymphocyte counts, and mild effects on the kidneys) in dogs were observed only at very high exposures compared with the clinical exposure (exposure ratio >38x the clinical exposure for the hepatic encephalopathy indication and >400x the clinical exposure for the travellers' diarrhoea indication).

No hepatotoxicity was observed at exposure ratios up to 93 for hepatically impaired patients taking Xifaxan 550 mg bid. The new study with different form rifaximin with higher systemic exposure provides reassurance for the use of rifaximin-α in hepatically impaired patients with higher systemic exposures than in other patient populations.

[3] van der Waaij D. (1986) The influence of the intestinal microflora on the relative thymus weight. *Med Microbiol Immunol.* 175: 335-40.

Nonclinical summary and conclusions

Summary

- The nonclinical dossier comprised data previously submitted and evaluated in the sponsor's original application to register rifaximin for the prevention of recurrence of hepatic encephalopathy, and a new repeat-dose dog study in dogs (a post marketing requirement by the US Food and Drug Administration [FDA]).
- The proposed indication is supported by previously evaluated nonclinical pharmacology studies. *In vitro* studies demonstrated activity of rifaximin against a range of anaerobic bacteria of the faecal flora, as well as against enteropathogens causing travellers' diarrhoea. The development of resistance was no greater than that observed with related antibiotics, such as rifampicin. *In vivo* in rats, rifaximin inhibited most aerobic species and total anaerobic cocci at dose levels below the clinical dose.
- The new 6 month repeat dose dog toxicity study achieved exposures considerably higher than exposures achieved by a different form of rifaximin. The exposures in dogs dosed with different form rifaximin were ≥ 38 fold higher than the clinical exposure in hepatically impaired patients taking 1100 mg/day and >400 fold higher than the expected clinical exposure in patients treated for travellers' diarrhoea at 600 mg/day.
- Thymus involution was observed in male dogs dosed with different form rifaximin and rifaximin-α in the new study, consistent with previously reported findings. Other findings in dogs treated with different form rifaximin (achieving relatively high plasma drug levels) were decreases in white blood cell and lymphocyte counts in males, and reductions in red blood cell count and minimal mineralisation of the ovaries and interstitial inflammation of the kidneys in female dogs. The findings with different form rifaximin with animal/human exposure ratios of ≥ 38 (based on AUC) were limited to the high dose group. There were no signals of hepatotoxicity.

Conclusion and recommendation

- Nonclinical data support the proposed indication.
- The new toxicity study in dogs does not raise additional safety concerns for patients with hepatic impairment taking 1100 mg/day Xifaxan for the prevention of recurrence of hepatic encephalopathy or for the new indication in patients with travellers' diarrhoea at 600 mg/day.
- Of reassurance is that no hepatotoxicity was observed in dogs at exposures up to 93 fold higher than the exposure in hepatically impaired patients taking 1100 mg/day Xifaxan.
- There are no nonclinical objections to the proposed dosing regimen for the treatment of travellers' diarrhoea, or to the continued registration of Xifaxan for the prevention of recurrence of hepatic encephalopathy.
- The current risk management plan (RMP) does not mention the results of the carcinogenicity studies in rodents or the 6 month repeat dose toxicity study in dogs. It is recommended that the results of these studies are documented in the safety specifications section of the RMP.

IV. Clinical findings

Introduction

This is a submission to extend the indications of rifaximin.

Clinical rationale

According to the sponsor, the chemical development programme of rifaximin began in the early 1980s, when the originator company (Alfa Wassermann SpA) was looking for a non-absorbable derivative of rifamycin with the same broad spectrum activity as rifampicin to develop in the treatment of GI disease due to external bacteria (infective diarrhoea) or resident bacteria (such as hepatic encephalopathy). Rifaximin was the compound selected for clinical development due to the broad antibacterial spectrum it demonstrated *in vitro* and its lack of absorption found in nonclinical studies.

The rationale for a non-absorbable drug aimed at treating intestinal diseases due to external bacteria and at managing diseases due to resident bacteria was for reasons of safety (lack of systemic effect) and microbiological resistance (unlike systemically acting antimicrobial agents, a non-absorbed drug would not select resistant bacteria outside its site of action). The sponsor was of the opinion that the optimal antibacterial treatment targeted against bacteria confined to the GI lumen should be non-absorbable antibiotics with a broad bactericidal spectrum, which reach the bacteria located in the intestinal tract, while being poorly or negligibly absorbed into the systemic circulation. According to the sponsor, while there are currently a number of non-absorbable antibiotics available which act against either gram-positive or gram-negative bacteria, rifaximin is the only non-absorbable antibiotic that acts against the main aerobic and anaerobic gram positive and gram negative bacteria, and has no other use outside the GI tract.

Travellers' diarrhoea (acute infectious diarrhoea associated with travel to developing tropical regions by residents of industrialised countries) affects 100 million people worldwide each year.

The two most common pathogens are enterotoxigenic *Escherichia* (*E.*) *coli* (ETEC) and enteroaggregative *E. coli* (EAEC), while invasive bacterial pathogens such as *Shighella spp.*, *Salmonella spp.* and *Campylobacter* (*C.*) *jejuni* account for about 15% of cases. The sponsor acknowledged that travellers' diarrhoea is a self-limiting disease in healthy adults, but is of the opinion that there is a need for pharmacological treatment options as travellers are often unwilling to wait for spontaneous improvement due to a busy travel schedule or require fast relief in order to make the most of their time abroad. Although quinolones are usually the antibiotics of choice in travellers' diarrhoea, they are often ineffective against Campylobacter, and in addition, as quinolones are also indicated in diseases such as urinary and respiratory tract infections, their use in the treatment of diarrhoea could select resistant bacterial strains in these sites.

Guidance

The sponsor had addressed the issues identified as requiring sponsor action in the TGA Planning Letter. These pertain to the TGA's request for the sponsor to tabulate the differences in the current dossier and the dossier previously provided for the registered strength of rifaximin.

Contents of the clinical dossier

The submission contained the following clinical information:

- 19 clinical pharmacology studies, including 11 that provided pharmacokinetic data
- 4 pivotal efficacy/safety studies (ESID0201, ESID9802, ESID9701 and ESID9601; Study ESID9601 was a pilot, dose-finding study)
- 18 other efficacy/safety studies (7 controlled studies, and 11 uncontrolled studies).
- 8 studies evaluating rifaximin paediatric formulation, 21 microbiology studies, 54 studies relating to other indications, Integrated Summary of Efficacy, Integrated Summary of Safety

The clinical pharmacology studies and some of the microbiology studies have been previously submitted and evaluated. In addition, some of the microbiology studies are related to other indications and not pertaining to the proposed indication of treatment of travellers' diarrhoea. In this evaluation report, as per the TGA Statement of Requirement to the clinical evaluator, focus will be placed only on studies that provide evidence to support the proposed indication (that is, treatment of travellers' diarrhoea) and the statements in the proposed PI. In addition, as per the TGA Statement of Requirement to the clinical evaluator, studies previously submitted and evaluated, studies relating to indications other than the currently proposed one, and studies conducted with different formulations other than the currently proposed one, will not be evaluated.

Paediatric data

The submission included paediatric efficacy/safety data (8 clinical studies evaluating efficacy and safety in paediatric population using rifaximin paediatric formulation). In this submission, the sponsor is not proposing the use of rifaximin in a paediatric population or the registration of the paediatric formulation. As per the TGA Statement of Requirement to the clinical evaluator, these studies will not be evaluated for the purpose of this submission.

Good clinical practice

The four pivotal clinical studies reviewed in this evaluation were in compliance with TGA guidelines.[4]

Pharmacokinetics

Studies providing pharmacokinetic data

All pharmacokinetic studies submitted for this application have been evaluated previously. A comparison of the currently approved Australian PI for rifaximin and the proposed PI showed that all statements included in the "Pharmacology" section of the proposed PI are present in the currently approved PI. The sponsor is not proposing to include any new clinical pharmacology information in the new PI.

Evaluator's conclusions on pharmacokinetics

Not applicable.

[4] ICH Harmonised Tripartite Guideline, "Note for Guidance on Good Clinical Practice (E6) (CPMP/ICH/135/95)", 10 June 1996.

Pharmacodynamics

Studies providing pharmacodynamic data

Several *in vitro* studies evaluated the antimicrobial activity of rifaximin against pathogenic bacterial strains isolated from faecal samples obtained from patients with diarrhoea in various developing countries. The rifaximin MIC_{50}, MIC_{90}, and MIC ranges for pathogens from these studies are summarised in Table 4. With regards to the interpretation of the MIC in relation to the clinical dose of rifaximin, the sponsor had stated that PK studies had shown that faecal concentrations[5] of rifaximin measured one day after a 3 day rifaximin 400mg bid dosing regimen yielded a mean concentration of about 8000 µg rifaximin/g faeces (range 777-15503 µg/g), equivalent to 8000 µg rifaximin/mL.

Table 4: Summary of MIC_{50}, MIC_{90}, and MIC ranges of rifaximin for travellers' diarrhoea clinical isolates.

Organism	No. of Strains	µg/mL		MIC Range[a]	Study
		MIC_{50}	MIC_{90}		
Aeromonas spp	27	12.5	100	12.5->200	PD9501
Aeromonas spp	17	16	64	16-512	PD0105
Aeromonas spp	3	16	16	8-16	PD0104
Campylobacter spp	35	>200	>200	0.195->200	PD9501
Campylobacter jejuni	24	128	256	0.25-512	PD0105
Campylobacter spp	11	32	64	8-64	PD0104
Enteroaggregative *E. coli*	65	8	16	4-32	PD0103
Enteroaggregative *E. coli*	62	64	128	8-128	PD0105
Enterohemorrhagic *E. coli*	17	50	>200	25->200	PD9501
Enteroinvasive *E. coli*	20	50	100	6.25->200	PD9501
Enteropathogenic *E. coli*	21	8	16	4-16	PD0103
Enterotoxigenic *E. coli*	44	8	16	1-32	PD0103
Enterotoxigenic *E. coli*	153	50	100	6.25->200	PD9501
Enterotoxigenic *E. coli*	77	64	64	4-1024	PD0105
Enterotoxigenic *E. coli*	347	32	64	0.098-512	PD0104
Hep-2 adherent *E. coli*	50	50	100	12.5->200	PD9501
Plesiomonas shigelloides	25	50	200	12.5->200	PD9501
Plesiomonas shigelloides	30	32	128	16-256	PD0105
Plesiomonas shigelloides	2	4	8	4-8	PD0104
Salmonella spp	53	50	100	6.25->200	PD9501
Salmonella spp	47	64	128	32-256	PD0105
Salmonella spp	32	32	50	6.25-64	PD0104
Shigella dysenteriae	4	4	8	4-8	PD0103
Shigella flexneri	78	4	8	2-16	PD0103
Shigella sonnei	4	4	16	8-16	PD0103
Shigella spp	88	50	100	25->200	PD9501
Shigella spp	65	64	128	2-256	PD0105
Shigella spp	27	32	64	0.098-256	PD0104
Vibrio cholerae	25	100	100	6.25-100	PD9501
Vibrio spp	18	32	128	2-128	PD0105
Vibrio spp	5	16	32	8-32	PD0104
Total or Range	1476	0.001–128	0.005–256	<0.001-1024	

Two *in vitro* studies compared the activity of rifaximin to that of standard antimicrobial agents against pathogens causing travellers' diarrhoea. In one study (PD0103), the antimicrobial activity of rifaximin against pathogenic bacteria was compared with that of 7 standard antimicrobial agents. Results showed that rifaximin had a MIC_{50} of between 4

[5] As rifaximin is essentially unabsorbed and the therapeutic site of action is the GI tract, the clinically relevant concentration would be that in the contents of the intestine, rather than blood concentration.

and 8 µg/mL and MIC_{90} of between 4 and 16 µg/mL for all pathogen strains except *Yersinia* (*Y.*) *Enterocolitica* and *C. jejuni*. The rifaximin MIC_{50} and MIC_{90} for *Y. Enterocolitica* were 64 and 128 µg/mL, respectively, while those for *C. jejuni* were 256 and 512 µg/mL, respectively. Overall, the activity of rifaximin was considered comparable to that of the other 7 antimicrobial agents for all enteropathogens tested except for *C. jejuni* (rifaximin MIC_{90} of 512 µg/mL). In the other study (PD0101), the antimicrobial activity of rifaximin against pathogenic bacteria was compared with that of 10 standard antimicrobial agents. Results showed that rifaximin inhibited 90% of the 284 bacterial enteropathogens causing travellers' diarrhoea at 32 µg/mL, which was 250 times lower than the mean rifaximin concentration found in stool in pharmacokinetic studies after a 3 day rifaximin 400mg bid dosing regimen (8000 µg rifaximin/mL). Of the 10 other standard antimicrobial agents tested, ciprofloxacin, levofloxacin, ceftriaxone, and azithromycin demonstrated good *in vitro* activity against the enteropathogens tested, but the more traditional antimicrobials such as ampicillin, trimethoprim, and trimethoprim/sulphamethoxazole (TMP/SMX) showed high levels and high frequencies of resistance. Amdinocillin, nalidixic acid, and doxycycline showed moderate activity.

An *in vitro* study (PD0106) was conducted to assess enterococcal resistance to rifaximin and cross resistance to rifampin using faecal isolates obtained from clinical study ESID9802 in patients treated for 3 days with rifaximin for travellers' diarrhoea (study treatments: rifaximin 600mg/day [200 mg tid.; 9 subjects], rifaximin 1200mg/day [400 mg tid; 10 subjects] or placebo [8 subjects]). Overall, 27 coliforms were identified biochemically as *E. coli*, the most common pathogen responsible for travellers' diarrhoea. For both rifaximin and rifampin, the MIC values obtained against the Day 0 (pre-treatment) and Day 3 (end of treatment) isolates were similar,[6] showing that resistance to rifaximin or cross-resistance to rifampin did not occur in enterococcus or *E. coli* following the 3 day duration of treatment with rifaximin.

An important consideration in the clinical use of rifaximin is the potential development of *Mycobacterium* (*M.*) *tuberculosis* cross resistance to rifampin after administration of rifaximin to treat GI infections in patients harbouring strains of *M. tuberculosis*. An *in vitro* study (PD9702) was conducted to evaluate the possible development of cross resistance to rifampin after incubation of *M. tuberculosis* strains with rifaximin. Five *M. tuberculosis* strains (3 pulmonary and 2 renal) isolated from man were incubated in vitro with ascending concentrations of rifaximin comparable to, or much greater than, those observed systemically after oral treatment (6, 20, 90, 270 ng/ml). The MICs of rifaximin and rifampin before and after incubation with rifaximin were identical, showing that no resistant *Mycobacteria* were selected.

The effect of rifaximin on normal intestinal flora in healthy volunteers was investigated in Study PD8601. Ten healthy volunteers were administered 400 mg rifaximin bid for 5 days and gram positive and gram negative aerobic and anaerobic normal faecal bacteria were examined for resistance to rifaximin by broth and agar dilution methods. Approximately 30-90% of the isolated strains developed resistance to rifaximin after 5 days of treatment. However, resistant strains disappeared rapidly from the intestinal flora when treatment was discontinued, more rapidly in aerobic strains and more slowly in anaerobic bacteria. Three months after the end of treatment no resistant strains could be detected in the faeces.

Evaluator's conclusions on pharmacodynamics

Results from the microbiological studies showed that rifaximin had antimicrobial activity against enteropathogens causing travellers' diarrhoea, with MIC_{50} and MIC_{90} levels within

[6] The pre- and post-treatment MIC90 for coliforms growing on rifaximin- or rifampicin-containing agar was 64 mg/L, in all 3 treatment groups (rifaximin 200 mg t.i.d., 400 t.i.d. or placebo).

the expected mean rifaximin faecal concentration after a 3 day rifaximin 400 mg bid dosing regimen. Although the proposed dose for the new indication in this submission is that of rifaximin 200 mg tid (that is, 600mg/day) for 3 days and not 400 mg bid, the dosing regimen from which rifaximin faecal concentration was measured of 400 mg bid for 3 days (that is, 800 mg/day) was close to the proposed dosing regimen. In addition, the MIC_{90} level was found to be 250 times lower than the mean rifaximin faecal concentration based on this dosing regimen of 400 mg bid. It is considered acceptable to use the mean rifaximin faecal concentration after a 3 day rifaximin 400 mg bid dosing regimen as an indication that the rifaximin MIC_{90} levels for the enteropathogens causing travellers' diarrhoea would be within the expected mean rifaximin faecal concentration after the recommended therapeutic dose.

Resistance studies results suggested that resistance to rifaximin or cross resistance to rifampin did not occur in enterococcus or *E. coli* following a 3 day duration of treatment with rifaximin (600 mg/day and 1200 mg/day). Resistant strains of normal intestinal flora developed after a 5 day treatment regimen with rifaximin (800 mg/day), but the effect was transient and the resistant strains disappeared rapidly from the intestinal flora when treatment was discontinued.

It is noted that the sponsor has included in the proposed PI, under the section of "Precautions" a statement that:

> *If symptoms have not resolved after 3 days of treatment, or recur shortly afterwards, a second course of Xifaxan should not be administered.*

It has also been indicated in the "Dosage and administration" section of the proposed PI that:

> *Xifaxan should not be used for more than 3 days even if symptoms continue. A second course of treatment must not be taken.*

This is considered appropriate, with regards to the microbiological results submitted.

Dosage selection for the pivotal studies

In this submission, 4 clinical studies were submitted as pivotal studies (studies ESID0201, ESID9802, ESID9701 and ESID9601). Of these studies, Study ESID9601 was the first pilot, proof-of-efficacy, Phase II dose finding study for the use of rifaximin in travellers' diarrhoea, and was initiated in 1996 in Mexico. The standard treatment for travellers' diarrhoea at that time was TMP/SMX, and 3 doses of rifaximin (200 mg tid, 400 mg tid and 600 mg tid) were compared against TMP/SMX in this study. The results indicated that rifaximin 200 mg tid was effective and well tolerated in patients with travellers' diarrhoea. This study also showed that the higher doses of rifaximin (400 mg tid and 600 mg tid) were well tolerated, but did not achieve substantial additional efficacy compared to rifaximin 200 mg tid.

According to the sponsor, after completion of this Phase II study, ciprofloxacin became the new standard treatment for travellers' diarrhoea, and hence a Phase III study was initiated in 1997 in Mexico and Jamaica comparing rifaximin with ciprofloxacin (Study ESID9701). As the previous Study ESID9601 testing rifaximin 600 mg/day (200 mg tid), 1200 mg/day (400 mg tid) and 1800 mg/day (600 mg tid) showed that there was no clearly superior dose of rifaximin in terms of efficacy, an intermediate dose of 800 mg/day rifaximin was chosen to be tested in this study. A twice daily regimen (that is, 400 mg bid) was chosen in order to conform to the double blind/double dummy study design (the active control ciprofloxacin was dosed at 500 mg bid) and to ensure good subject acceptance and compliance. Rifaximin 400 mg bid was shown to be as efficacious as ciprofloxacin in reducing the duration of travellers' diarrhoea.

Following this study and after preliminary scientific consultation with the FDA, a Phase III placebo controlled study was initiated in 1998 in Mexico, Kenya and Guatemala evaluating 2 doses of rifaximin (200 mg tid and 400 mg tid)(Study ESID9802) These doses were chosen in order to compare results with the first pilot dose finding study (ESID9601). In addition, given the high rate of GI motility of patients with travellers' diarrhoea, administration three times a day was considered preferable to twice daily. Study results showed that both doses of rifaximin were more effective than placebo with comparable efficacy shown between the 2 rifaximin doses.

Following further consultation with the FDA, a second Phase III placebo controlled and active controlled study was performed in 2002 comparing rifaximin 200 mg tid to placebo and to ciprofloxacin (Study ESID0201). According to the sponsor, the daily rifaximin dose of 200 mg tid had been specifically requested by the FDA in its 25 October 2002 Approvable Letter as the dose to be used in a confirmatory second Phase III trial. This study involved centres in India in order to evaluate more cases of diarrhoea due to invasive bacteria (*Campylobacter spp., Shigella spp.* and *Salmonella spp.*) as too few cases had been evaluated in the previous study to be able to draw any definite conclusions about the efficacy of rifaximin against these bacteria.

Efficacy

Studies providing efficacy data

Four pivotal efficacy studies were submitted. Three of these were Phase III, randomised, multi centre, double blind studies of 3 day treatment regimens of rifaximin in adult patients with travellers' diarrhoea (Study ESID0201 compared rifaximin [200 mg tid] with placebo and ciprofloxacin [500 mg bid]; Study ESID9802 compared 2 doses of rifaximin [200 mg tid and 400 mg tid] with placebo; Study ESID9701 compared rifaximin [400 mg bid] with ciprofloxacin [500 mg bid]). One study (ESID9601) was a Phase II, randomised, multi centre, double blind study of 5 day treatment regimens of rifaximin in adult patients with travellers' diarrhoea, comparing rifaximin (200 mg tid, 400 mg tid or 600 mg tid) with TMP/SMX (160 mg TMP/800 mg SMX bid).

In this evaluation report, Study ESID0201, comparing the efficacy of the proposed clinical dose regimen of rifaximin 200 mg tid for 3 days against placebo, will be considered the main pivotal study to be evaluated, and will be presented first. Study ESID9802 will be evaluated with regards to further supporting data for the proposed clinical dose of rifaximin 200 mg tid Study ESID9701 will be evaluated with regards to additional data comparing rifaximin to ciprofloxacin, and Study ESID9601 will be evaluated as a dose finding study to support the dose of rifamixin tested in Study ESID0201.

Evaluator's conclusions on efficacy

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal studies were appropriate. The study primary and secondary endpoints allowed evaluations of clinical (rapidity of return to normal formed stools and the resolution of symptoms) and microbiological effects. Baseline demographic and disease characteristics were comparable among treatment groups in each study, and were consistent with the target patient population.

Primary efficacy analysis in Study ESID0201 showed that the median time to last unformed stool (TLUS) with rifaximin 200 mg tid treatment for 3 days was statistically significantly shorter than that with placebo (32.0 h versus 65.5 h, $p = 0.0014$). This was supported by the primary efficacy analysis results in Study ESID9802 which also showed that the median TLUS with rifaximin 200 mg tid for 3 days was statistically significantly

shorter than that with placebo (32.5 h versus 60.0 h, p = 0.0001). Median TLUS with rifaximin in Studies ESID9701 and ESID9601 were consistent with these results (median TLUS of 25.7 h for rifaximin 400 mg bid for 3 days [Study ESID9701] and 26.25 h for rifaximin 200 mg tid for 5 days [Study ESID9601]).

In terms of clinical symptoms, results in Study ESID0201 showed that there was a statistically significantly smaller number of unformed stools passed after the first dose of study medication with rifaximin compared to placebo (p = 0.0002). Over the entire study period (0 to 120 h), the mean number of unformed stools passed was 8.8 with rifaximin, compared with 9.7 with placebo. A statistically significantly higher proportion of subjects in the rifaximin group than the placebo group showed improvement in diarrhoeal syndrome during the 48 to 72 h interval (89.1% versus 79.5%, p = 0.0346) and the 72 to 96 h interval (92.9% versus 83.8%, p = 0.0250). There was a statistically significantly higher proportion of subjects achieving wellness with rifaximin compared to placebo (76.6% versus 61.4%, p = 0.0039), and a statistically significantly lower proportion of subjects with treatment failure with rifaximin compared to placebo (14.7% versus 26.7%, p = 0.0115). These results were supported by those in Study ESID9802, showing that overall, there was a statistically significantly smaller number of unformed stools with rifaximin 200mg tid compared to placebo (p = 0.0001). A statistically significantly higher proportion of subjects had improvement in diarrhoeal syndrome in the rifaximin 200 mg tid group versus the placebo group in the 24-48 h interval (87.1% versus 72.9%, p = 0.007) and in the 48-72 h intervals (91.3% versus 78.8%, p = 0.008). There was a statistically significantly higher proportion of subjects achieving wellness with rifaximin 200 mg tid compared to placebo (79.2% versus 60.5%, p = 0.001), and a statistically significantly lower proportion of subjects with treatment failure with rifaximin 200 mg tid compared to placebo (16.0% versus 34.9%, p = 0.001).

With regards to dose selection, results supported the choice of rifaximin 200 mg tid dose regimen. Initial preliminary uncontrolled, pilot studies (ESID8201 and ESID8202) assessed 3 doses of rifaximin: 400 mg/day (that is, 100 mg qid), 600 mg/day (200mg tid) and 800mg/day (200 mg qid), and both studies concluded that the higher doses were more efficacious (600-800 mg/day). Subsequent preliminary controlled studies (ESID8301 [active controlled; neomycin] and ESID8401 [placebo controlled]) tested rifaximin 600-800 mg/day and showed that stool frequency and consistency normalised in approximately 3 days in patients treated with rifaximin, and was about half the time taken by patients receiving placebo (p <0.05; study ESID8401) and comparable to neomycin (Study ESID8301).

Efficacy results in the dose finding Study ESID9601 showed that there was no obvious dose dependent trend over the rifaximin dose ranges tested (200 mg tid, 400 mg tid and 600 mg tid) and efficacy results were generally comparable with TMP/SMX. The median TLUS was 26.25, 40.50 and 35.00 in the rifaximin low, mid and high dose groups, respectively (versus 47.00 h in the TMP/SMX group), and the median number of unformed stools passed during the five days' observation was 4.0, 5.5 and 5.0, respectively (versus 5.0 in the TMP/SMX group). Improvement in diarrhoeal syndrome was noted for 55.6%, 44.4% and 52.6% of subjects, respectively (versus 58.8% in the TMP/SMX group) by the end of 24 h of treatment, and for 83.3%, 77.8% and 89.5%, respectively (versus 76.5% in the TMP/SMX group) by the end of 48 h of treatment. The proportion of subjects with treatment failure was 11%, 0% and 21%, respectively (versus 29% in the TMP/SMX group).

These results were supported by those of Study ESID9802 comparing rifaximin 200 mg tid and 400 mg tid against placebo. Results showed that the median TLUS in the rifaximin 200mg tid and 400 mg tid groups were comparable (32.5 and 32.9 h, respectively, versus 60.0 h with placebo; p = 0.0001 for both rifaximin 200 mg tid versus placebo, and rifaximin 400 mg tid versus placebo). The mean number of unformed stools passed per

time interval was comparable between the 2 rifaximin doses, as was the proportion of subjects with improvement in diarrhoeal syndrome across time intervals. The proportion of subjects achieving wellness was comparable between the rifaximin 200 mg tid and 400 mg tid groups (79.2% and 81%, respectively, versus 60.5% with placebo; p = 0.001 for both rifaximin 200 mg tid versus placebo, and rifaximin 400 mg tid versus placebo), as was the proportion of subjects with treatment failure (16.0% and 16.7%, respectively, versus 34.9% with placebo; p = 0.001 for both rifaximin 200 mg tid versus placebo, and rifaximin 400 mg tid versus placebo).

Comparison of rifaximin with standard treatment for travellers' diarrhoea (ciprofloxacin) showed that results were generally comparable between the 2 treatments. In Study ESID0201, the median TLUS in the rifaximin 200 mg tid (32.0 h) and ciprofloxacin 500 mg bid (28.8 h) groups was comparable.

There was no statistically significant difference in the proportion of subjects achieving wellness between the rifaximin and ciprofloxacin groups (76.6% versus 78.2%, p = 0.7388). However, there was a statistically significantly smaller number of unformed stools passed after the first dose of study medication with ciprofloxacin compared to rifaximin (p<0.0001). Over the entire study period (0 to 120 h), the mean number of unformed stools passed was 6.2 with ciprofloxacin, compared with 8.8 with rifaximin. The proportion of intention to treat (ITT) subjects with improvement in diarrhoeal syndrome was also numerically higher in the ciprofloxacin group compared to rifaximin group across time intervals. There was a statistically significantly lower proportion of subjects with treatment failure with ciprofloxacin compared to rifaximin (6.9% versus 14.7%, p = 0.0483).

However, additional efficacy analyses showed that when subjects with signs and symptoms suggestive of inflammatory/invasive pathogens (that is, fever and/or blood in the stool at baseline) were excluded, efficacy analyses between rifaximin and ciprofloxacin became comparable across more efficacy endpoints (median TLUS: 23.3 h with rifaximin versus 27.4 h with ciprofloxacin; proportion of subjects achieving wellness: 87.1% versus 80.0%, p = 0.3058; proportion of subjects with treatment failure: 8.6% versus 7.7%, p = 0.6742). In addition, there was no statistically significant difference in the number of unformed stools between the rifaximin and Cipro groups in this restricted population (p = 0.4113). Over the entire study period (0 to 120 h), the mean number of unformed stools passed was 7.0 with rifaximin, compared with 5.6 with ciprofloxacin.

Results in Study ESID9701 comparing rifaximin 400 mg bid with ciprofloxacin 500 mg bid also showed comparable results between the 2 treatments. The median TLUS were comparable (25.7 h for rifaximin versus 25.0 h for ciprofloxacin). There was no statistically significant difference in the proportion of subjects with improvement in diarrhoeal syndrome between the rifaximin and Cipro groups during the 0-24 h interval (58.1% versus 63.1%, p = 0.419) and during the 24-48 h interval (82.8% versus 85.1%, p = 0.667). The proportion of subjects achieving wellness was comparable between the rifaximin and Cipro groups (87.1% versus 88.3%, p = 0.803), as was the proportion of subjects with treatment failure (9.7% versus 5.7%, p = 0.258).

Efficacy analyses in terms of microbiological eradication showed that the proportion of subjects with microbiological eradication across all pathogens was comparable between 3 day regimen of rifaximin 200 mg tid and placebo (Study ESID0201: 61.6% with rifaximin versus 51.7% with placebo, p = 0.1952 [80.7% with ciprofloxacin; ciprofloxacin versus placebo: p = 0.0008]; Study ESID9802: 68.6% with rifaximin versus 67.2% with placebo). By pathogen, the microbiological eradication rate for diarrhoeagenic *E. coli* in the MITT population in Study ESID0201 was also comparable between 3 day regimen of rifaximin 200 mg tid and placebo (74.7% with rifaximin group versus 69.8% with placebo, p=0.5344; 95.6% with ciprofloxacin [ciprofloxacin versus placebo: p = 0.0015]). Pathogen eradication rates for *E. coli* from pooled studies ESID9601, ESID9701 and ESID9802 was

75% of patients in the pooled rifaximin group (85.7% in the pooled control group [placebo as well as active controls]). However, it is clinically recognised that microbiological eradication is not necessarily correlated to clinical improvement in travellers' diarrhoea. Analyses looking at correlation between microbiologic and clinical outcome generally supported this. In Study ESID0201, median TLUS was similar among rifaximin treated subjects achieving wellness, regardless of whether pathogens were eradicated or persisted (23.4 versus 25.8 h). Pooled data from Studies ESID9601, ESID9701 and ESID9802 also showed that median TLUS was similar for rifaximin treated patients with ETEC eradication and those who failed to eradicate pre-treatment ETEC strains (30.75 versus 32.50 h, p = 0.530).

Microbiological analyses results also suggested that rifaximin had greater clinical and microbiologic efficacy in subjects with diarrhoeagenic *E. coli* compared to subjects with inflammatory/invasive pathogens (*C. jejuni, salmonella, shigella*). In Study ESID0201, among subjects culture positive for diarrhoeagenic *E. coli*, clinical wellness was achieved in 84.5% of subjects and microbiological eradication was reported in 77.3% of subjects. Among subjects culture positive for inflammatory/invasive pathogens, clinical wellness was achieved in 42.5% of subjects and microbiological eradication was reported in 52.5% of subjects. The median TLUS in the ITT population was 24.0 h in rifaximin treated subjects with diarrhoeagenic *E. coli* while the median TLUS could not be calculated in rifaximin treated subjects with inflammatory/invasive pathogens as more than half of these subjects failed to achieve wellness.

It is noted that the proposed indication for the submission is for the "treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria". In addition, the sponsor has included in the proposed PI, under the section of "Precautions" a statement that:

> *Clinical data have shown that rifaximin is not effective in the treatment of travellers' diarrhoea caused by invasive enteric pathogens such as Campylobacter spp., Salmonella spp. and Shigella spp., which typically produce dysentery-like diarrhoea characterised by fever, blood in the stool and high stool frequency.*

This is considered appropriate with regards to the efficacy results submitted.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies (Studies ESID0201, ESID9802, ESID9701 and ESID9601)

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit.
- Laboratory tests performed included haematology and urinalysis. Studies ESID9802 and ESID9601 also assessed clinical chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], and creatinine).

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

The sponsor submitted 18 supporting efficacy/safety studies, as described in Section 7.1.2 of this evaluation report. The safety data of the studies relevant to this submission were evaluated and did not raise any safety concerns.

Patient exposure

In Study ESID0201, the mean number of days on study drug across the treatment groups was 3.6 and exposure ranged from 1 to 5 days. Overall, 73.9% of patients in the rifaximin group had an exposure of ≥ 4 days. In Study ESID9802, between 79% and 85% of subjects in each treatment group (placebo, rifaximin 600mg/day and rifaximin 1200mg/day) received all 9 doses. Exposure data was not presented in the clinical study report (CSR) for Study ESID9701, but compliance data showed that out of the 18 tablets that each subject should have taken over the 3-day treatment duration, the mean (SD) number of tablets taken was 17.7 (1.7) and 17.6 (2.2) in the rifaximin and Cipro groups, respectively. In study ESID9601, patients treated with rifaximin were exposed to treatment for an average of 4.98 ± 0.4 days and 5.92 g of active substance each, that is, a total exposure of 328.7 g in 274 patient-days of treatment. These data are compounded from a total exposure of 56.6 g in 95 patient-days at the dose of 600 mg/day, of 107.2 g in 90 patient-days at the dose of 1200 mg/day, and of 160g in 89 patient-days at the dose of 1800 mg/day. The patients treated with TMP/SMX have been exposed to treatment for an average of 4.83 ± 0.8 days and 9.2 g of active substance each; that is, a total exposure of 156.7 g in 82 patient-days.

> *Comments: Overall, the study drug exposure is adequate to assess the safety profile of rifaximin.*

Post marketing data

The sponsor had provided 3 periodic safety update reports (PSURs) covering the periods 23 April 1985 (date of first international authorisation of rifaximin) to 31 May 2011, 29 November 2012 to 29 May 2013, and 30 May 2013 to 29 November 2013. These PSUR did not lead to significant safety concerns.

Evaluator's conclusions on safety

Overall, safety results did not raise any major safety concerns and are consistent with known safety profile of rifaximin. Safety results of rifaximin submitted in this application are consistent with those reported in the currently approved Australian PI for rifaximin. Results in the pivotal studies were generally comparable between rifaximin and placebo. In Study ESID0201, the percentages of subjects with any AEs (26.6% with rifaximin 200 mg tid versus 25.0% with placebo), treatment related AEs (10.6% versus 10.0%), serious AEs (SAEs) (0.5% versus 1.0%), and AEs leading to discontinuation of study drug (2.0% versus 2.0%) were comparable between the rifaximin and placebo groups. This was supported by results in Study ESID9802, showing that the percentage of subjects with any AEs was 71.8% with rifaximin 200 mg tid versus 75.2% with placebo, and the percentage of subjects with any treatment related AEs was 59.7% with rifaximin 200 mg tid versus 69.8% with placebo. No subject in the rifaximin 200 mg tid group reported any SAE, compared with 1 in the placebo group. One subject in the rifaximin 200 mg tid group reported an AE leading to discontinuation of study drug, compared with none in the placebo group.

Comparison of rifaximin with standard treatment for travellers' diarrhoea (ciprofloxacin) showed that safety results in the pivotal studies were generally comparable between the 2 treatments. In Study ESID0201, the percentages of subjects with any AEs (26.6% with rifaximin 200 mg tid versus 24.0% with ciprofloxacin 500 mg bid), treatment related AEs

(10.6% versus 14.0%), SAEs (0.5% versus 0%), and AEs leading to discontinuation of study drug (2.0% versus 3.0%) were comparable between the rifaximin and ciprofloxacin groups. This was supported by results in Study ESID9701 comparing rifaximin 400 mg bid with ciprofloxacin 500 mg bid, showing that the percentage of subjects with any AEs was 33.3% with rifaximin versus 36.2% with ciprofloxacin, and the percentage of subjects with any treatment related AEs was 10.8% with rifaximin versus 16.0% with ciprofloxacin (p = 0.296). No subjects in either group reported any SAEs. No subject in the rifaximin group reported any AE leading to discontinuation of study drug compared with 1 in the ciprofloxacin group.

Safety results submitted in this application are consistent with known safety profile of rifaximin. Analyses on pooled data from Studies ESID0201 and ESID9802, comparing rifaximin 200 mg tid with placebo, showed that the most commonly reported treatment related AE by preferred term in the pooled rifaximin group was flatulence (9.7% with rifaximin versus 19.3% with placebo, p = 0.1034) and headache (5.3% versus 5.7%, p = 0.8100).

First round benefit-risk assessment

First round assessment of benefits

The benefits of rifaximin in the proposed usage for treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria are:

- Broad spectrum antibiotic that acts locally in the GI lumen with minimal systemic absorption is of clinical benefit.

Although travellers' diarrhoea is generally a self-limiting disease in healthy adults, pharmacological treatments which shorten the duration of illness and reduce morbidity can have economic and social benefits. When antibiotics are used in the treatment of diarrhoea, quinolones such as ciprofloxacin are usually the antibiotics of choice. However, the use of systemic antibiotics could increase the risk of systemic adverse effects as well as antibiotic resistance. Hence, the availability of a broad spectrum antibiotic that acts locally in the GI lumen with minimal systemic absorption is of clinical benefit.

Efficacy results supported the efficacy of a 3 day regimen of rifaximin 200 mg tid over placebo in terms of rapidity of return to normal formed stools and the improvement of symptoms.

- There was a statistically significantly shorter median TLUS with rifaximin 200mg t.i.d. treatment for 3 days compared with placebo (Study ESID0201: 32.0 h versus 65.5 h, p = 0.0014; Study ESID9802: 32.5 h versus 60.0 h, p = 0.0001).
- There was a statistically significantly smaller number of unformed stools passed after the first dose of study medication with rifaximin compared to placebo in both Study ESID0201 (p = 0.0002) and Study ESID9802 (p = 0.0001).
- In Study ESID0201, a statistically significantly higher proportion of subjects in the rifaximin group than the placebo group showed improvement in diarrhoeal syndrome during the 48 to 72 h interval (89.1% versus 79.5%, p = 0.0346) and the 72 to 96 h interval (92.9% versus 83.8%, p = 0.0250). In Study ESID9802, a statistically significantly higher proportion of subjects had improvement in diarrhoeal syndrome in the rifaximin 200 mg tid group versus the placebo group in the 24-48 h interval (87.1% versus 72.9%, p = 0.007) and in the 48-72 h intervals (91.3% versus 78.8%, p = 0.008).
- There was a statistically significantly higher proportion of subjects achieving wellness with rifaximin compared to placebo (Study ESID0201: 76.6% versus 61.4%, p =

0.0039; Study ESID9802: 79.2% versus 60.5%, p = 0.001), and a statistically significantly lower proportion of subjects with treatment failure with rifaximin compared to placebo (Study ESID0201: 14.7% versus 26.7%, p = 0.0115; Study ESID9802: 16.0% versus 34.9%, p = 0.001).

In addition, the minimal systemic absorption of rifaximin has contributed to a largely benign safety profile.

First round assessment of risks

The risks of rifaximin in the proposed usage are:

- GI symptoms, for example, flatulence and constipation
- Headache

Overall, safety results did not raise any major safety concerns and are consistent with known safety profile of rifaximin. Safety results of rifaximin submitted in this application are consistent with those reported in the currently approved Australian PI for rifaximin. In addition, results in the pivotal studies were generally comparable between rifaximin and placebo.

Analyses on pooled data from Studies ESID0201 and ESID9802 comparing rifaximin 200 mg tid with placebo showed that the most commonly reported treatment-related AE by preferred term in the pooled rifaximin 200 mg tid group was flatulence (9.7% with rifaximin versus 19.3% with placebo, p = 0.1034) and headache (5.3% versus 5.7%, p = 0.8100). Overall, the AEs (all causality) of flatulence and headache were of mostly of mild or moderate in intensity. Severe flatulence was reported in 1.3% of subjects in the pooled rifaximin group (versus 3.9% in pooled placebo group), while severe headache was reported in 0.6% in the pooled rifaximin group (versus 0.9% in pooled placebo group).

First round assessment of benefit-risk balance

The benefit-risk balance of rifaximin, given the proposed usage, is favourable.

Efficacy results supported the efficacy of 3-day regimen of rifaximin 200 mg tid over placebo in terms of rapidity of return to normal formed stools (median TLUS of 32 to 33 hours with rifaximin compared with 60 to 66 h with placebo p≤ 0.0014) as well as the improvement of symptoms (statistically significantly smaller number of unformed stools passed; statistically significantly higher proportion of subjects with improvement in diarrhoeal syndrome; statistically significantly higher proportion of subjects achieving wellness; statistically significantly lower proportion of subjects with treatment failure).

Overall, safety results did not raise any major safety concerns, were generally comparable between rifaximin and placebo, and are consistent with known safety profile of rifaximin.

First round recommendation regarding authorisation

It is recommended that the application to extend the indications of rifaximin for the use of rifaximin 200 mg tablets for the treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria, be approved. This is subject to satisfactory response to the queries raised.

Clinical questions

None

Second round evaluation of clinical data

Not applicable

Second round benefit-risk assessment

Not applicable

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU Risk Management Plan (EU-RMP) (Version: 2.0, dated 20 June 2014) with an Australian Specific Annex (ASA) Version 1.1, dated November 2014.

The initial RMP documentation submitted in support of this submission was inadequate. Consequently, there was no Round 1 evaluation phase, but rather only a Section 31 request for information or documents (as it relates to the RMP) was sent to the sponsor. Subsequently, the sponsor submitted acceptable RMP documentation, which was evaluated during the Round 2 evaluation phase.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Ongoing safety concerns.

Summary of safety concerns	
Important identified risks	• *Clostridium Difficile* Associated Diarrhoea (CDAD) • Allergic reactions
Important potential risks	• *New drug-drug interactions* • *Cross-resistance to rifampicin* • *Off-label use in unauthorised indications* • *Off-label use in the paediatric population*
Missing information	• *No data in the paediatric population*

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities consistent with the "Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines", to monitor all the specified ongoing safety concerns.

The ASA states that a post authorisation drug utilisation study requested by the UK Medicines and Healthcare products Regulatory (MHRA) for rifaximin 200 mg tablets for use in the treatment of travellers' diarrhoea has now been completed. The sponsor's correspondence dated November 2014 states that the results of this study have been included in the updated EU-RMP for the 200 mg tablet and have been summarised as follows:

> *Sixteen percent of patients were taking Rifaximin 200 mg on-label for traveller's diarrhoea, with the remaining 84% of patients were assessed to be taking Rifaximin 200 mg 'off label' for non-traveller's diarrhoea related diagnoses. However, it is worth noting that the majority of Rifaximin prescriptions were dispensed between 2011 and 2012, that is, prior to the launch of the Rifaximin 550 mg product in 2013 which is indicated for use in patients to reduce the recurrence of episodes of hepatic encephalopathy in people at least 18 years of age who have liver disease.*

It is reassuring to note that less than 2% of patients were found to be taking Rifaximin under the age of 18 years (that is, 'off-label'), the majority of whom were taking Rifaximin for non-traveller's diarrhoea related conditions.

Eighteen percent of patients (n = 60) were identified as receiving concomitant medications with the potential for drug-drug interactions, but the vast majority of these were taking Rifaximin for non-traveller's diarrhoea related illnesses. Omeprazole was by far the most common concomitant medication, followed well behind by warfarin and anti-epileptic medications, each taken by 6 patients.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important potential risk: 'Cross-resistance to rifampicin' for which no risk minimisation activities are proposed.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no objections on chemistry and quality control grounds to the registration of the proposed 200 mg rifaximin tablets. The evaluator commented that Good Manufacturing Practice (GMP) clearances for the drug substance manufacturer and finished product manufacturer are current; however, they are due to expire prior to the conclusion of the expected decision phase.

Nonclinical

The nonclinical data supported the proposed indication. There were no nonclinical objections to the proposed dosing regimen for the treatment of travellers' diarrhoea, or to the continued registration of Xifaxan for the prevention of recurrence of hepatic encephalopathy.

The nonclinical dossier comprised data previously submitted and evaluated in the sponsor's original application to register rifaximin for the prevention of recurrence of hepatic encephalopathy and a new repeat-dose dog toxicity study. Only the **new** study was reviewed in this evaluation report.

The new toxicity study in dogs did not raise additional safety concerns for patients with hepatic impairment taking 1100 mg/day Xifaxan for the prevention of recurrence of hepatic encephalopathy or for the new indication in patients with travellers' diarrhoea at 600 mg/day. No hepatotoxicity was observed in dogs at exposures up to 93 fold higher than the exposure in hepatically impaired patients taking 1100 mg/day Xifaxan.

The nonclinical evaluator recommended that the safety specifications section of the current RMP include the results of the carcinogenicity studies in rodents and the 6 month repeat dose toxicity study in dogs.

Clinical

There was a significant amount of overlap with the previous submission for the 550 mg tablet for prevention of recurrent hepatic encephalopathy). As per the TGA statement of

requirements, the clinical evaluation focused on studies to support the proposed indication of treatment of travellers' diarrhoea, with studies previously evaluated or those related to other indications or formulations not considered.

Pharmacology

All pharmacokinetic studies submitted for this application had been evaluated previously. The sponsor is not proposing to include any new clinical pharmacology information in the revised PI.

In vitro studies evaluated the antimicrobial activity of rifaximin against pathogenic bacterial strains isolated from faecal samples obtained from patients with diarrhoea in various developing countries. The rifaximin MIC_{50}, MIC_{90}, and MIC ranges for pathogens from these studies are summarised in Table 4.

The evaluator concluded that results from the microbiological studies showed that rifaximin had antimicrobial activity against enteropathogens causing travellers' diarrhoea, with MIC_{50} and MIC_{90} levels within the expected mean rifaximin faecal concentration after a 3 day rifaximin 400 mg bid dosing regimen (that is, 800 mg/day), with this dose being close to the proposed dosage regimen (600 mg/day).

The UK public assessment report and clinical evaluator noted the limitations of these data in relation to clinical outcomes for treatment of travellers' diarrhoea, given the local gut concentrations of rifaximin may be very high and potentially overcome some of the acquired resistance mechanisms.

Efficacy

Four pivotal efficacy studies were submitted (Table 6). Three studies (ESID0201, ESID9802 and ESID9701) were Phase III, randomised, multicentre, double blind studies of 3 day treatment regimens of rifaximin in adult patients with travellers' diarrhoea. Study ESID9601 was a Phase II, randomised, double blind, dose finding study of a five day treatment with rifaximin, comparing three dose regimens with a standard regimen of trimethoprim/sulfamethoxazole.

Table 6: Overview of evaluated studies.

Study, location, year completed	Study design	Comparator	Study population and age range	Number of patients randomised	Primary efficacy endpoint	Duration of follow-up
ESID0201 Mexico, India, Guatemala, Peru 2003	Phase III, randomised, multicentre, double-blind	Placebo, ciprofloxacin	Adults ≥ 18 years with acute diarrhoea	399 197:rifaximin 101: placebo 101: ciprofloxacin	Comparison of TLUS between rifaximin and placebo	5 days
ESID9802, Mexico, Kenya, Guatemala, 2000	Phase III, randomised, multicentre, double-blind	Placebo	Adults ≥ 18 years with acute diarrhoea	380 129:placebo 125: rifaximin 200mg tid 126: rifaximin 400mg tid	Comparison of TLUS between rifaximin and placebo	5 days
ESID9701 Mexico, Jamaica, 1998	Phase III, randomised, multicentre, double-blind	Ciprofloxacin	Adults ≥ 18 years with acute diarrhoea	187 93: rifaximin 94: ciprofloxacin	Comparison of TLUS between rifaximin and ciprofloxacin	5 days
ESID 9601 Mexico,1996	Phase II, randomised, multicentre double-blind, dose-finding	Trimethoprim/ sulfamethoxazole	Adults ≥ 18 years with acute diarrhoea	76 19 in each rifaximin dose group 19: TMP/SMX group)	Comparison of TLUS between rifaximin and TMP/SMX	8 days

TLUS: time to last unformed stool
TMP/SMX: trimethoprim/sulfamethoxazole

Study ESID0201: comparison with placebo and ciprofloxacin

Study ESID0201 was a randomised, double blind, multi centre, placebo and active controlled study comparing rifaximin with placebo and with ciprofloxacin in the treatment of travellers' diarrhoea due to enteropathogenic organisms.

The primary objective was to assess the safety and efficacy of rifaximin compared to placebo in the treatment of travellers' diarrhoea due to enteropathogenic organisms. Eligible subjects were randomly assigned to 1 of 3 treatment groups (rifaximin 200 mg tid, placebo, or ciprofloxacin 500 mg bid in a 2:1:1 ratio) to be treated with study medication for 3 days.

The primary efficacy endpoint was TLUS, after which wellness was declared. The primary efficacy outcome was the TLUS for rifaximin compared to placebo. Secondary efficacy outcomes and endpoints are described in the clinical evaluation report and included the comparison of rifaximin to ciprofloxacin with respect to TLUS.

Of 399 participants enrolled and randomised, a total of 355 subjects completed the study (177 [89.8%], 84 [83.2%] and 94 [93.1%] in the rifaximin, placebo and ciprofloxacin groups, respectively).While baseline demographic characteristics were comparable among treatment groups in the ITT population, disease characteristics differed, with a higher proportion of subjects in the rifaximin group culture-positive at baseline for inflammatory/invasive pathogens (23.4%; 46/197) compared to the ciprofloxacin group (12.9%; 13/101).

Primary efficacy analysis showed that the median TLUS in the rifaximin group was statistically significantly shorter than that in the placebo group (32.0 h versus 65.5 h in the placebo group, p = 0.0014).

The median TLUS in the rifaximin (32.0 h) and ciprofloxacin (28.8 h) groups was comparable. Further results are described in the clinical evaluation report. Clinical efficacy (in terms of median TLUS) for subjects with inflammatory/invasive pathogens was poor in all treatment groups. For this subgroup, the evaluator commented that more than half of the subjects in the rifaximin group failed to achieve wellness and therefore median TLUS

could not be calculated, while median TLUS in the placebo and ciprofloxacin groups were 67.5 and 65 h, respectively.

In the overall ITT population, the proportion of treatment failures in the rifaximin group was approximately double that in the Ciprofloxacin group (14.7% versus 6.9%). When subjects with fever and/or blood in the stool at baseline were excluded, the proportion of treatment failures in the rifaximin and Ciprofloxacin groups were comparable (8.6% versus 7.7%).

Study ESID 9802: comparison with placebo

Study ESID9802 was a randomised, double blind, multi centre, parallel, comparative, placebo controlled study which compared 2 doses of rifaximin (200 mg tid [600 mg/day] and 400 mg tid [1200 mg/day]) versus placebo in the treatment of bacterial infectious diarrhoea in travellers. The primary objective was to assess the safety and efficacy of rifaximin as compared to placebo in the treatment of infectious diarrhoea in travellers. Primary and secondary endpoints were the same as those for Study ESID0201.

Of 380 subjects enrolled and randomised, a total of 344 subjects completed the study (110 [85.3%], 115 [92.0%] and 119 [94.4%] in the placebo, rifaximin 600 mg, and rifaximin 1200 mg groups, respectively).

Primary efficacy analysis showed that the median TLUS in the rifaximin 600 mg and 1200mg groups were 32.5 and 32.9 h, respectively, compared with 60.0 h in the placebo group ($p = 0.0001$) for both rifaximin 600 mg versus placebo, and rifaximin 1200 mg versus placebo. Results of the analysis of TLUS for the "Efficacy evaluable" population were similar to those in the ITT population.

Study ESID 9701: comparison with ciprofloxacin

Study ESID9701 was a randomised, double blind, double dummy study comparing a 3 day regimen of 800 mg/day of rifaximin (400 mg bid) against a standard 3 day regimen of 1000 mg/day of ciprofloxacin (500 mg bid) in the treatment of travellers' diarrhoea. The objectives were to compare the clinical efficacy (based on TLUS), microbiological outcome (that is, eradication of the causative organism), and relative safety and tolerability of rifaximin with a standard regimen of ciprofloxacin.

Of 187 subjects enrolled and randomised, a total of 182 subjects completed the study (92 [98.9%] and 90 [95.7%] in the rifaximin and ciprofloxacin groups, respectively).

The primary efficacy analysis showed that the median TLUS for the ITT population was 25.7 hours for rifaximin and 25.0 hours for ciprofloxacin. Overall, analyses of the secondary efficacy endpoints showed that there were no statistically significant differences between treatment groups for the secondary efficacy endpoints except for the incidence of nausea over 24-48 h and 48-72 h intervals (statistically significantly lower in the rifaximin group compared to the ciprofloxacin group), and the incidence of tenesmus over 0-24 h (statistically significantly higher in the rifaximin group compared to the ciprofloxacin group).

The proportion of subjects with microbiological cure was presented. Results showed that among subjects with a pathogen or pathogens at pre-treatment the proportion of subjects with microbiological cure was 32.3% and 41.5% in the rifaximin and ciprofloxacin groups, respectively ($p = 0.441$).

Study ESID 9601: dose-finding study

Study ESID9601 was a Phase II, randomised, double blind, double dummy, parallel, dose response study comparing 3 dose regimens of rifaximin (200 mg tid, 400 mg tid and 600 mg tid) against a standard regimen of TMP/SMX (160/800 mg bid)

The objectives were to compare the activity of 3 dose regimens of rifaximin to one another in order to determine the most effective dose for the treatment of travellers' diarrhoea, to assess the effectiveness of the 3 dose regimens for eradication of causative organisms, to assess the relative safety and tolerability of these 3 regimens, and to compare the rifaximin treatments to a standard treatment regimen of TMP/SMX for the treatment of travellers' diarrhoea.

A total of 76 subjects were enrolled and randomised: 19 to each of the 4 treatment groups. A total of 72 subjects completed the study (18 in each of the rifaximin groups, and 17 in the TMP/SMX group). Among the rifaximin groups, there were no obvious dose dependent trends in the efficacy endpoints.

Overall, the evaluator concluded that results from the clinical studies supported the rifaximin 200 mg tid dose regimen. This dose had been specifically requested by the FDA in 2002 for further Phase III trials.

Safety

Safety results of rifaximin submitted in this application were consistent with those reported in the currently approved Australian PI for rifaximin.

The evaluator commented that comparison of rifaximin with standard treatment for travellers' diarrhoea (ciprofloxacin) showed that safety results in the pivotal studies were generally comparable between the two treatments. In Study ESID0201, the percentages of subjects with any AEs (26.6% with rifaximin 200 mg tid versus 24.0% with ciprofloxacin 500 mg bid), treatment related AEs (10.6% versus 14.0%), SAEs (0.5% versus 0%), and AEs leading to discontinuation of study drug (2.0% versus 3.0%) were comparable. This was supported by results in Study ESID9701.

Analyses on pooled data from studies ESID0201 and ESID9802, comparing rifaximin 200 mg tid with placebo, showed that the most commonly reported treatment related AE in the pooled rifaximin group was flatulence (9.7% with rifaximin versus 19.3% with placebo, p = 0.1034) and headache (5.3% versus 5.7%, p = 0.8100).

There were no deaths reported in Studies ESID0201, ESID9802, ESID9701 and ESID9601. Three PSURs were provided, covering the periods 23 April 1985 (date of first international authorisation of rifaximin) to 31 May 2011, 29 November 2012 to 29 May 2013, and 30 May 2013 to 29 November 2013. These reports did not lead to significant safety concerns.

It is noteworthy that the UK MHRA public assessment report commented that given the short duration of follow-up, the safety databases from the traveller diarrhoea studies were not designed to assess long term safety of rifaximin and specifically the potential to select for *C. difficile* enterocolitis. While patients with hepatic encephalopathy and other conditions in which rifaximin have been studied have received longer courses of treatment, collection of safety data in these studies was generally inadequate. Furthermore, despite the apparent lack of major safety issues and given the large number of doses administered, lack of spontaneous reporting may have contributed to this.

Section 31 response: concomitant administration with loperamide

There was no Round 2 clinical evaluation report, as the issues raised by the Clinical Evaluator following Round 1 were able to be reviewed by the TGA with the Section 31 response. The clinical evaluator requested further information in regards to the use of anti-motility agents (for example, loperamide) together with rifaximin, given concomitant use is likely to be recommended during an acute episode of diarrhoea.

Information provided from a sponsored randomised, double blind study P5F[7] (Salix Pharmaceuticals Inc.) of 310 patients with travellers' diarrhoea who received rifaximin alone (n = 102), loperamide (n = 104) or rifaximin and loperamide combination therapy (n = 104) showed that rifaximin and rifaximin-loperamide significantly reduced the median time until passage of the last unformed stool (32.5 ± 4.14 h and 27.3 ± 4.13 h, respectively) versus loperamide (69 ± 4.11 h; p = 0.0019). The mean number of unformed stools passed during illness was lower with rifaximin-loperamide compared with either agent alone. Treatments were well tolerated and the incidence of adverse events was low for all groups.

The wording proposed by the sponsor in the "Interactions" section of the PI is supported by these data.

RMP evaluation

A revised ASA (Revision 1.2, February 2015) was submitted with the notification to the TGA of errors/omissions in evaluation reports on the 24 February. The RMP evaluator was satisfied that all RMP recommendations had been satisfactorily addressed, however the ASA may need further revisions following the Advisory Committee on Prescription Medicines (ACPM) and the final PI/ Consumer Medicine Information (CMI) negotiations.

The submission was not presented to the Advisory Committee on the Safety of Medicines (ACSOM).

Risk assessment of microbial resistance

This assessment was presented according to the format requested by the TGA.

Key points include:

- Development of resistance is similar to that with rifampicin, which is primarily due to a chromosomal one-step alteration in the drug target, DNA dependent RNA polymerase.
- While rifaximin is relatively similar to rifampicin in that mutations may occur rapidly with use, this is not considered to be an issue with rifaximin since the α polymorph used in Xifaxan is minimally absorbed and present in a very high concentration in the GI tract.
- No Australian resistance data is available and the sponsor understands that rifaximin resistance is not routinely tested for.
- Rifaximin is a low risk for the emergence of cross-resistance to rifampicin. The committee is requested to comment on the data in relation to the European reports.
- A 'low risk' category has been assigned for the risk characterisation for Xifaxan.
- The sponsor estimates that there will be 20,000-30,000 units sold per annum. Reimbursement from the Pharmaceutical Benefits Scheme (PBS) for Xifaxan 200 mg tablets will not be sought.

[7] Dupont HL, et al. (2007) Treatment of travelers' diarrhea: randomized trial comparing rifaximin, rifaximin plus loperamide, and loperamide alone. *Clin Gastroenterol Hepatol.* 5: 451-6.

Risk-benefit analysis

Delegate's considerations

The submission includes sufficient data in regards to efficacy and safety to extend the indication for Xifaxan to the treatment of travellers' diarrhoea. Prior approval by the FDA (2004) and MHRA (2010) is relevant. The availability of post marketing data (since initial registration 30 years ago) provides further reassurance regarding safety, noting some limitations of the safety database to detect long term or delayed adverse effects, given the short duration of therapy.

Comparison of rifaximin with standard treatment for travellers' diarrhoea (ciprofloxacin) demonstrated that results were generally comparable between the two treatments. Rifaximin had greater clinical and microbiologic efficacy in subjects with *E. coli* compared to subjects with inflammatory/invasive pathogens such as *Campylobacter, Salmonella and Shigella* species. This has been adequately reflected in the proposed PI.

The evaluated studies were completed more than ten years ago. Given the changing patterns of antibiotic resistance and recommended therapies, the choice of active comparator (ciprofloxacin) was appropriate at the time, but may be less relevant for people currently travelling to certain regions in Asia. ACPM comment is sought regarding this.

The sponsor's assessment with regards to the risk of antibiotic resistance with the use of rifaximin is acknowledged and appears sound, with ACPM comment specifically sought regarding this issue.

Proposed action

Pending advice from the ACPM, the Delegate proposes to register Xifaxan rifaximin 200 mg film coated tablets for the treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria. As a condition of registration, the EU-RMP (Version: 2.0, dated 20 June 2014), revised as specified by the ASA (Revision: 1.2, dated February 2015), must be implemented.

The submitted data support the efficacy and safety to extend the indication for Xifaxan to the treatment of travellers' diarrhoea. Xifaxan has been registered internationally since 1985. With regards to antibiotic resistance, a 'low risk' category has been assigned by the sponsor.

The sponsor is requested to address the following issues with the pre ACPM response:

- Please provide an update of the overseas regulatory status.
- Please provide an update regarding submission of studies in children for Xifaxan in Europe and the US. The FDA approved indication includes the treatment of patients ≥12 years of age. What is the sponsor's intention with respect to Australia, given the submission to the TGA included paediatric data?
- Please ensure that GMP clearances are current at the time of the expected decision phase.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- Please comment on the Antibacterial Risk Assessment data.

- Does the committee agree with the sponsor's assessment of a 'low risk category'? Are there plausible biological reasons why a non-absorbed antibiotic is likely to have a lower level of clinically relevant resistance?
- Is there any need to specifically monitor antibiotic resistance in Australia?
- The role for rifaximin and its place in therapy, in light of currently recommended treatments (azithromycin or norfloxacin).

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Norgine is in agreement with the proposed actions of the Delegate that Xifaxan 200 mg tablets should be registered *for the treatment of adult patients with travellers' diarrhoea caused by non-invasive enteric bacteria*.

GMP clearance

All GMP clearances are now current throughout the expected decision phase.

Children

The sponsor has not sought an indication that includes use in children, as the four pivotal studies in travellers' diarrhoea did not include subjects under 18 years. This is consistent with the indication for travellers' diarrhoea obtained in the United Kingdom.

However, the prescribing information in the USA, Germany and Denmark permits use in subjects ages over 12 years of age.

The originator company, Alfa Wassermann (AW), will not be conducting or submitting any new paediatric studies with rifaximin 200 mg. However, AW does intend to publish a meta-analysis prepared from past rifaximin paediatric studies. Based on this meta-analysis, the rifaximin SPC in Germany and Denmark includes the following statement:

> *Paediatric population*
>
> *The efficacy, posology and safety of rifaximin in paediatric patients younger than 12 years of age have not been established. Literature review identified 9 efficacy studies in the paediatric population which have included 371 children, 233 having received rifaximin. Most of the enrolled children were aged more than 2 years. The characteristic which was present in all studies was diarrhoea of bacterial origin (proven before, during or after treatment). The data (the studies per se and a meta-analysis) show that there is a positive trend to demonstrate efficacy of rifaximin in a special condition [acute diarrhoeas (mainly recurrent or relapsing) which are known or supposed to be caused by non-invasive rifaximin sensitive bacteria such as Escherichia coli].*
>
> *The most commonly used dosage in children from 2-12 years in these limited studies with few patients was in the range of 20-30 mg/kg/d divided in 2 to 4 doses (see section 4.2).*

United States

In April 2003, the FDA issued a written request to Salix (the US licence holder) for data on paediatric patients (>3 to < 16 years old) with TD/acute diarrhoea with suspected bacterial aetiology. Salix is in the process of compiling the study report for a bioavailability study with rifaximin oral suspension and micro-tablets (based on a new solid state dispersion formulation) for paediatric use. Additionally, Salix is finalising a protocol to study the efficacy, safety and pharmacokinetics of the micro-tabs formulation in children. The protocol will require review by the FDA Paediatric Review Committee before Salix can

proceed with the study. According to currently approved (extended) timelines, this study must complete by 2018.

Accordingly, the sponsor does not anticipate submitting future data to the TGA to support the use of rifaximin 200 mg tablets for the treatment of travellers' diarrhoea in children less than 18 years of age.

We note that when the sponsor's application for rifaximin 550 mg tablets for the prevention of recurrence of hepatic encephalopathy was reviewed by the ACPM in 2012, the Delegate proposed removal of the word 'adult' from the proposed indication, while including a statement within the PI that safety and efficacy had not been established in patients under 18 years. This proposal was subsequently adopted. A similar course of action remains available for this application if considered appropriate.

Bacterial resistance

The sponsor acknowledges that there are concerns about the potential for development of bacterial resistance to rifaximin, and consequences for other members of the rifamycin group, and rifampicin in particular. However, there are a number of factors that reduce this risk;

- Rifaximin, present as the alpha polymorph, is poorly absorbed from the gut (<1%)
- Rifaximin achieves high concentrations in the gut, greatly exceeding the MICs of sensitive organisms
- Minimal systemic absorption means bacteria outside the gut are not exposed to selective pressure
- Resistance to rifaximin is not plasmid mediated
- Some studies suggest rifaximin resistant organisms have lower viability
- Use in this proposed indication is for 3 days only

The primary mechanism for the development of resistance to rifaximin is a chromosomal one step alteration in the drug target, DNA dependent RNA polymerase. Target site alterations are caused by mutations in the rpoB gene, which encodes for bacterial DNA dependent RNA polymerase. This mechanism differs from the plasmid mediated resistance that is easily acquired by susceptible bacteria after treatment with aminoglycosides, sulphonamides and macrolides.

The issue of resistance was considered by the ACPM when it reviewed the application to register rifaximin 550 mg tablets in 2012. At the time, the sponsor stated we believed that the development of clinically significant microbial resistance was unlikely, and had not previously been reported over the greater than 20 year period rifaximin has been in use. The proposed new indication is for a lower dose, and is restricted to a single 3 day course, compared to six month or longer treatment for hepatic encephalopathy. The potential for development of resistant organisms is addressed in the risk management plan.

C. difficile infection

The Delegate's overview referred to comments in the rifaximin 200 mg MHRA public assessment report that collection of longer term safety data in studies of patients with hepatic encephalopathy was generally inadequate. This was written prior to the publication of the pivotal Phase III rifaximin HE study (Bass, RFHE3001) and its open label extension study (RFHE3002) which followed patients up to 24 months.

In the Bass study, there were 2 cases of *C. difficile* diarrhoea in the rifaximin group (n = 140) over the 6 month study. Both patients had several concurrent risk factors for *C. difficile* infection, and were treated successfully, while remaining on rifaximin. In the open label extension of the Bass study (2) up to 2 years, a further 4 cases occurred, also in

subjects with concurrent risk factors. All responded to standard treatment. The incidence of *C. difficile* in these studies is consistent with known rates for patients with decompensated cirrhosis and use of rifaximin does not raise additional concerns in this patient group. It should be noted that rifaximin is sometimes used to treat *C. difficile* infection that has not responded to, or relapsed after standard antibiotic treatment.

Place of antibiotics in treatment of travellers' diarrhoea

Travellers' diarrhoea affects a large proportion of travellers to developing countries. Standard preventative advice includes avoidance of risk factors, often summarised as:

> *"Boil it, cook it, peel it or forget it."*

Antibiotic prophylaxis is generally not recommended as it would lead to widespread antibiotic use of quinolones and macrolides and a more rapid development of resistance. The focus should therefore be on non-antibiotic preventative measures, with appropriate use of a single short course of antibiotic treatment. Current agents recommended include quinolones and azithromycin, but there is increasing resistance to quinolones reported. Evidence suggests that use of rifaximin is less likely to contribute to the development of resistance than use of systemically absorbed antibiotics.

While travellers' diarrhoea is generally mild and self-limiting, it impacts negatively on a sufferer's holiday, business or sporting program. Episodes of travellers' diarrhoea have also been shown to be associated with a greater risk of developing irritable bowel syndrome. Rifaximin has been shown to be effective and well tolerated in the treatment of travellers' diarrhoea caused by non-invasive enteric bacteria, and offers a non-systemic antibiotic option as an alternative to existing antibiotic treatments.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy advised that Xifaxan film coated tablets, containing 200 mg of rifaximin has an overall positive benefit-risk profile for the following modified indication:

> *Xifaxan is indicated for the treatment of patients (≥12 years of age) with travellers' diarrhoea caused by non-invasive strains of Escherichia coli (see PRECAUTIONS, CLINICAL TRIALS).*

In making this recommendation, the ACPM:

- Advised that the indication be consistent with the results from the clinical trials that rifaximin is not effective and should not be used in patients with invasive pathogens as clearly expressed in an indication similar to that recommended by EU countries.
- Advised that the data submitted (pending the Delegates' review of requested additional data) are adequate to support use in subjects over 12 years of age, noting that other countries such as the USA, Germany and Denmark allow use in subjects over 12 years of age.

Proposed conditions of registration

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

PI/ CMI amendments

The ACPM proposed the following amendments to the PI/CMI:

- In the PRECAUTIONS section, a statement should be added that Xifaxan should not be used in patients with diarrhoea complicated by fever or blood in the stool or diarrhoea due to pathogens other than *E. coli*.

- Addition, in table format, of microbiological eradication rates with and without invasive pathogens for each of the studies and the location where each study was undertaken
- The CMI should be reformatted to give advice to the consumer when self-medicating rather than referral to a health professional for advice; a suitable health professional may not be accessible when travelling overseas.
- Further information in the CMI is required about drug interactions with rifaximin (for example, oral contraceptive pill, warfarin, and cyclosporin).
- The CMI should provide a clear explanation on instances when it is not appropriate to use rifaximin, that is, in invasive diarrhoea.

Specific advice

The ACPM advised the following in response to the specific delegate's questions on this submission:

- Please comment on the Antibacterial Risk Assessment data.

The ACPM advised that the Antibacterial Risk Assessment data underestimate the current and potential risk. The ACPM noted that there were few resistant strains in the clinical trials and in vitro resistance was under emphasised. The ACPM considered the argument that high concentrations in the faeces of rifaximin reduce the risk of resistance is hypothetical and does not justify the paucity of microbiological resistance data.

- Does the committee agree with the Sponsor's assessment of a 'low risk category'? Are there plausible biological reasons why a non-absorbed antibiotics likely to have a lower level of clinically relevant resistance?

The ACPM did not agree with the proposed low risk resistance category. The ACPM considered that the impact of use of the drug by a significant and travelling population, the impact of potential cross resistance to rifampicin on the treatment of tuberculosis, and the impact of *C. Difficile* and *E. coli* resistance in Australia had not been considered.

The ACPM noted that the risk of resistance of organisms causing travellers' diarrhoea depends on the aetiology and sensitivity of organisms in specific regions. The ACPM noted that South East Asia has a high level of resistance for *salmonella, shigella, campylobacter* and *E. coli* and that Asia has three times the incidence of *campylobacter* in travellers than other regions. The ACPM noted that the clinical trials were conducted in regions such as Central America, Africa and India which have a different incidence of invasive disease to many areas of SE Asia, a common Australian traveller destination. Rifaximin could be considered as an alternative in travel to areas **not** involving Asia and where there is a low incidence of *campylobacter*. This should be incorporated in the indications or precautions section of the PI and included in the CMI.

The ACPM noted that Australians travel frequently to Asia and are exposed to resistant organisms as well as travellers' diarrhoea that is more likely to be invasive. The impact of resistance to rifaximin could be significant as rifaximin is used off label in Australia to treat *C. Difficile*. In addition, any impact on resistance to rifampicin would be clinically significant.

The ACPM also considered that there is no plausible biological reason that a non-absorbed antibiotic will have a lower level of clinical resistance.

- Is there any need to specifically monitor antibiotic resistance in Australia?

The ACPM advised that antibiotic resistance to rifaximin should be monitored in Australia, noting that any impact of cross resistance with rifampicin would be clinically significant.

The ACPM considered that the methodology for monitoring should be made available and the pattern of resistance elucidated in all indications for rifaximin.

- The role for rifaximin and its place in therapy, in light of currently recommended treatments (azithromycin or norfloxacin).

The ACPM considered the role and place of therapy of rifaximin would be as an alternative to azithromycin and quinolones for travellers to non-Asian/low *Campylobacter* regions. The ACPM advised that consumers and prescribers need to understand that rifaximin should not be used for invasive diarrhoea and that this could be partly achieved by having an indication which highlights when rifaximin should not be used such as that approved in some EU countries.

- The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACPM advised the addition, in table format, of microbiological eradication rates with and without invasive diarrhoeal pathogens for each of the studies in and the location where each study was undertaken.

The ACPM considered that the formatting of questions 'ask your doctor or pharmacist' needs to be addressed as it is completely inadequate. The consumer will likely be overseas when the questions arise, be self-medicating and not able to ask questions of their doctor/pharmacist. In addition, the ACPM noted that there was no information on drug interactions with rifaximin, such as the oral contraceptive pill, warfarin or ciclosporin. The ACPM advised that further information is needed for the consumer instead of just referring them to their doctor or pharmacist, who may not be readily available.

The CMI should also provide advice on when rifaximin is not indicated, consistent with ACPM's recommended indication.

The ACPM advised that 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 Xifaxan tablet containing rifaximin 200 mg indicated for:

> *Xifaxan is indicated for the treatment of patients (≥ 12 years of age) with travellers' diarrhoea caused by non-invasive strains of Escherichia coli (see 'PRECAUTIONS', and 'CLINICAL TRIALS').*
>
> *Travellers' diarrhoea describes a clinical picture predominantly observed in subjects travelling from developed to developing countries. It is most frequently caused by enterotoxigenic Escherichia coli (ETEC), enteroaggregative E. coli (EAEC) and other non-invasive pathogens.*

Specific conditions of registration applying to these goods

- The European RMP (Version: 2.0, dated 20 June 2014), revised as specified by the ASA (Revision: 1.2, dated February 2015), must be implemented for the Xifaxan rifaximin 200 mg tablet.

Attachment 1. Product Information

The PI approved for Xifaxan at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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