



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rifaximin

Proprietary Product Name: Xifaxan

Sponsor: Norgine Pty Ltd

November 2012

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I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	4 May 2012
Active ingredient(s):	Rifaximin
Product Name(s):	Xifaxan
Sponsor's Name:	Norgine Pty Ltd 3/14 Rodborough Road Frenchs Forest NSW 2086
Dose form(s):	Tablet, film-coated
Strength(s):	550 mg
Container(s):	Blister packs
Pack size(s):	14, 28, 30, 56 and 60
Approved Therapeutic use:	Prevention of the recurrence of hepatic encephalopathy where other treatments have failed or are contraindicated.
Route(s) of administration:	Oral
Dosage:	1 x 550 mg tablet twice daily with or without food
ARTG Number (s)	AUST R 183411

Product background

This AusPAR describes an orphan drug application to register Xifaxan (rifaximin) for the following indications:

Prevention of the recurrence of hepatic encephalopathy in adults.

The sponsor's orphan drug application is due to the low prevalence of hepatic encephalopathy (HE) in the Australian population. HE is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced and/or end stage liver disease (ESLD) of all aetiology. The neurological symptoms of HE are attributed to global central nervous system (CNS) depression from nitrogenous compounds and other gut derived neurotoxins that disrupt neurotransmitter regulation and therefore disrupt the transmission of key metabolic neuronal substrates resulting in neuronal dysfunction and encephalopathy. These nitrogenous compounds and gut derived neurotoxins are

by-products of endogenous bacterial metabolism in the gastrointestinal (GI) tract and gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. The most important of these compounds is thought to be ammonia, a by-product of protein digestion which is normally detoxified by the liver.

Current treatments for prevention of HE recurrence include:

1. Lactulose administered two to four times per day. Lactulose is a synthetic, non-digestible sugar which reduces faecal transit time by acting as an osmotic laxative. In the setting of HE, lactulose is metabolised in the colon by bacterial flora to short chain fatty acids including the production of the lactic acid and acetic acid. This partially dissociates, acidifying the colonic contents, favouring formation of the non-absorbable NH_4^+ from ammonia (NH_3), trapping NH_3 in the colon and effectively reducing plasma NH_3 concentrations. The reduction in ammonia formation is associated with a reduction in the risk of HE recurrence, however, diarrhoea is an almost invariable consequence of the use of lactulose for HE prevention.
2. Other approaches include the use of systemically absorbed antibiotics such as neomycin but this drug is hampered by aminoglycoside toxicity, that is, nephrotoxicity and ototoxicity with long-term use.

Rifaximin is a non-systemic, oral antibiotic derived from rifamycin, which has a broad spectrum of activity against Gram-positive and Gram-negative, aerobic and anaerobic enterobacteria. This class of antibiotics inhibits the Deoxyribonucleic acid (DNA) dependent ribonucleic acid (RNA) polymerase of susceptible microorganisms, leading to the suppression of initiation of chain formation during RNA synthesis. Rifaximin may also alter virulence factors of the gut bacterial pathogens without killing. When taken orally, less than 1% of the dose is absorbed from the GI tract. It could be viewed as a topical agent in the gut lumen.

Rifaximin has a broad spectrum of activity against many non-invasive GI pathogens and normal faecal flora. Variable schedules of oral dosing achieve very high levels of intra-luminal rifaximin well above the MIC₅₀ and MIC₉₀¹ for most of these organisms. There appears to be little to no selection of resistance although most data are derived from relatively short-term exposure to rifaximin, that is, in the setting of treatment or prevention of traveller's diarrhoea. Two mechanisms of rifaximin resistance exist and these are discussed under *Clinical Findings Pharmacodynamics* below. The risk of horizontal dissemination of rifaximin resistance to other bacteria is low. Spontaneous rifaximin-resistance has been reported in a number of gut organisms; enterococci, *Clostridium difficile*, *Clostridium perfringens* and *Bacteroides fragilis*. With respect to *C.difficile*, there is no cross resistance with rifaximin-resistance strains and metronidazole or vancomycin, the mainstay of *C.Difficile* diarrhoea treatment.

Regulatory status

The overseas regulatory status is summarised in Table 1 below.

¹The MIC₅₀ and MIC₉₀ are ways of recording antibiotic sensitivities more conveniently.

MIC₅₀=Minimum Inhibitory Concentration required to inhibit the growth of 50% of organisms.

MIC₉₀= Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms.

Table 1. Summary of overseas regulatory status. Table continued across two pages.Rifaximin 550 mg tablets for Hepatic Encephalopathy

Country	Submission	Approval	Status	Indication
United States	2009	March 2010	Approved	Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age
EU	September 2011		Under evaluation	Reduction in recurrence of episodes of hepatic encephalopathy in adults

Rifaximin 200 mg tablets for the treatment of travellers diarrhoea.

Country	Submission	Approval	Status	Indication
United States	Dec 2001	May 2004	Approved	The treatment of patients (≥ 12 years of age) with travelers' diarrhea (TD) caused by noninvasive strains of <i>Escherichia coli</i>
UK	Mar 2008	Dec 2010	Approved	Xifaxan 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.

Table 1 continued. Summary of overseas regulatory status.Rifaximin 550 mg tablets for the treatment irritable bowel syndrome

Country	Submission	Approval	Status	Indication
United States	June 2010	-	Rejected	Treatment of non-constipation irritable bowel syndrome (IBS), and IBS related bloating in patients > 18 years of age
The FDA issued a Complete Response Letter to Salix on 7 March 2011, confirming that their supplemental New Drug Application could not be approved, mainly due to absence of data on efficacy of repeat courses of treatment. In November 2011 the FDA Gastrointestinal Drugs Advisory committee agreed on a study design for a repeat treatment protocol, and this study was initiated in February 2012. The IBS dose is higher than the HE dose, and is 550 mg three times daily.				

Product Information

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

Abbreviations used in this AusPAR

Table 2. Abbreviations

AE	adverse event	LDH	lactate dehydrogenase
ALT	alanine transaminase	LC-MS/MS	liquid chromatography with tandem mass spectrometry
ANOVA	analysis of variance	MDZ	midazolam
AST	aspartate transaminase	MedDRA	Medical Dictionary for Regulatory Activities
ATP	adenosine-5'-triphosphate	MIC	minimum inhibitory concentration
AUC	area under the plasma concentration-time curve	MIC50	minimum inhibitory concentration that inhibits 50% of microorganism growth
BCRP	breast cancer resistance protein	MIC90	minimum inhibitory concentration that inhibits 90% of microorganism growth
BID	twice daily	MITT	Modified intention-to-treat
BSEP	bile salt export protein	MRP1	multidrug resistance protein 1
BUN	blood urea nitrogen	MRP2	multidrug resistance protein 2
CCr	calculated creatinine clearance	MRP4	multidrug resistance protein 4
		NA	not applicable
<i>C. difficile</i>	<i>Clostridium difficile</i>	NCT	Number connection test
CI	Confidence interval	PD	pharmacodynamic(s)
CL/F	apparent total body clearance	P-gp	P-glycoprotein
C _{max}	maximum observed plasma concentration	OC	Oral contraceptive
C _{min}	minimum observed plasma concentration or trough concentration at steady state	PEY	person exposure years
CNS	central nervous system	PCS	Potentially clinically significant
CV	coefficient of variation	PK	pharmacokinetic(s)
CYP3A4	cytochrome P450 3A4	PP	Per protocol
DM	Diabetes mellitus	PPB	Plasma protein binding
EE	ethinyl estradiol	PSE	portal-systemic encephalopathy
EEG	electroencephalogram	QD	once daily
EMA	European Medicines Agency	QTc	QT interval corrected for heart rate
ESLD	End-stage liver disease	Rc	Accumulation ratio
EAEC	enteroaggregative <i>Escherichia coli</i>	RBC	red blood cell
ETEC	enterotoxigenic <i>Escherichia coli</i>	RFX	RFX
FDA	Food and Drug Administration	RNA	ribonucleic acid
GCP	Good Clinical Practice	SAE	serious adverse event
GI	gastrointestinal	SD	standard deviation
GT	glutamyltransferase	SE	standard error
HE	Hepatic encephalopathy	SIBO	small intestinal bacterial overgrowth
hERG	human ether-à-go-go-related gene	TD	travellers' diarrhoea
IBS	irritable bowel syndrome	t½	half-life
IC50	50% inhibitory concentration	TID	three times daily
INR	international normalized ratio	TIPS	transjugular intrahepatic portosystemic shunt
ITT	intent-to-treat	T _{max}	time to maximum observed plasma concentration
IV	intravenous	UGT	UDP-glucuronosyltransferase
K	rate constant	Vd/F	apparent volume of distribution

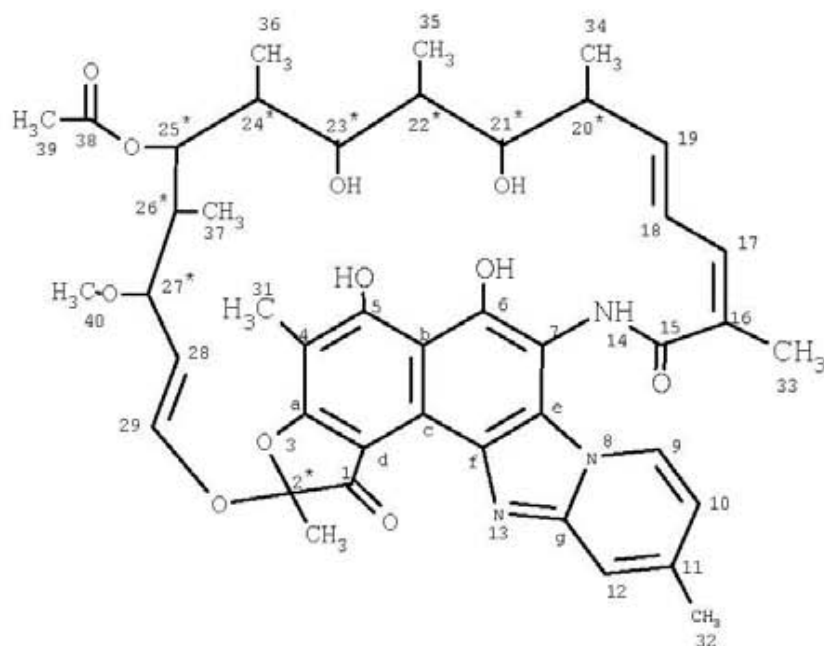
II. Quality findings

Drug substance (active ingredient)

The proposed new chemical entity, 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.

There is a European Pharmacopeia (Ph.Eur.)/British Pharmacopeia (BP) monograph for the drug substance, rifaximin.

Rifaximin is a red-orange crystalline powder that is insoluble in water. The structure of rifaximin is shown in Figure 1 below.

Figure 1. Rifaximin structure

Rifaximin contains nine asymmetric carbons located at the following positions: C2, C20, C21, C22, C23, C24, C25, C26, C27. 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 (a, β , γ , d and e), have been isolated and identified by X-ray powder diffraction. However, only rifaximin a is obtained from the manufacturing procedure and is verified in the proposed drug substance specification using x-ray diffraction techniques. This is critical as forms γ and d exhibit significant systemic absorption.

Rifamycin B is produced by fermentation, then oxidised to rifamycin O, which is reacted with 2-amino-4-methylpyridine to give crude rifaximin. Crude rifaximin contains about 10% of an oxidised form (the 6,7-*ortho*-iminoquinone). Treatment with ascorbic acid reduces the iminoquinone back to rifaximin, which is purified by recrystallisation from aqueous ethanol.

Drug product

The drug product is a film-coated tablet for oral administration, containing 550 mg of rifaximin, packaged in heat-sealed polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC)/Aluminium (Al) blister packs. The tablets are manufactured by a conventional dry granulation process.

The recommended dose of Xifaxan is one 550 mg tablet twice daily, with or without food.

The specifications for both the active pharmaceutical ingredient (API) and finished product include limits for a number of specified impurities. The limits are generally in accordance with EU guidelines except for a limit of 0.5% applied to the sum of impurities D and H, which co-elute. The Medicines Toxicology Evaluation Section at TGA has advised that this limit has been adequately qualified.

The dissolution test included in the finished product specifications employs a paddle apparatus. The method is considered discriminatory, as evidenced by changes in dissolution rate observed during stability studies.

The company claimed a shelf life of 3 years below 25°C on the basis that three batches tested demonstrated compliance with specifications during 2 years' storage at 25°C/60% relative humidity (rh). However, there is a consistent and significant decrease in potency of the product under these storage conditions and statistical analysis of the data indicated that a shelf life of only 12 months was warranted.

Biopharmaceutics

Rifaximin is not intended to be absorbed systemically. It is intended to exert its effect locally in the gastrointestinal tract.

An absolute bioavailability study of rifaximin is not feasible because of the low solubility of the drug substance. Evidence of low systemic absorption of rifaximin is provided by Study RFPK9801. Following administration of a single oral 400 mg dose of radioactive carbon (¹⁴C)-labelled rifaximin in healthy subjects, only 0.32% of the dose was excreted in urine, approximately 10% of which was unchanged drug. The remainder of the dose was excreted in the faeces, almost completely as unchanged drug. The sponsor claims that the presence of most faecal radioactivity as ¹⁴C-rifaximin indicates poor absorption (it is claimed that as the small fraction of the dose absorbed was extensively metabolised, biliary excretion would be expected to result in the presence of metabolites of ¹⁴C-rifaximin in faeces). Furthermore, a study of the excretion of radioactivity in rat bile following oral administration of ¹⁴C-rifaximin showed that less than 2% of the dose is excreted by this route in the rat.

Studies on the effect of food on the systemic absorption of rifaximin showed that food increased the area under the plasma concentration time curve (AUC) approximately 2 fold but this is still considered negligible.

The drug was developed more than 20 years ago and was formulated as 200 mg tablets for the treatment of traveller's diarrhoea. At that time, polymorphism in rifaximin was unknown. However, studies during the period 2003-2006 revealed the existence of five polymorphic forms, which varied considerably in their bioavailability, presumably due to different solubilities (see following table).

Table 3.

Pharmacokinetic parameters (mean) for Rifaximin following single oral administration of 100 mg/kg by capsules to dogs

Polymorph	C _{max}	t _{max}	AUC _{0-t}	AUC _{0-inf}
	ng/ml	h	ng·h /ml	ng·h /ml
α	2.58	4	17	17
β	1.10	4	10	12
γ	1085.13	2	4795	4894
δ	308.31	2	801	830
ε	6.86	4	42	77

On the basis of the consistency of the drug substance manufacturing process over the years, the company assumes that the currently produced alpha form of rifaximin has always been produced. In particular, it is assumed that the alpha form was used in Study

RFPK9801. In clinical trials conducted since the existence of polymorphism was discovered, the drug has always been used as the alpha form. Evidence has been provided that the alpha form does not convert into other polymorphic forms during manufacture or storage of Xifaxan tablets.

Advisory committee considerations

The submission was considered by the TGA's Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 142nd meeting on 21 November 2011. The subcommittee endorsed the questions that had been raised by the Pharmaceutical Chemistry Section and made some comments concerning the product information (PI) document.

The PI has since been revised to address the comments of the PSC and the questions raised by the Pharmaceutical Chemistry Section have been satisfactorily addressed.

Quality summary and conclusions

The quality evaluator's concerns regarding decreases in rifaximin assay during storage of the tablets have not been assuaged. However, registration approval was recommended with a shelf life of 12 months below 25°C. (see addendum)

Addendum

Following receipt of the final quality evaluation report, the sponsor contacted the TGA to discuss the assigned shelf life of 12 months below 25°C. The sponsor accepted the evaluator's concerns regarding the significant decreases in assay values observed during stability studies but indicated that a shelf life of only 12 months would not be commercially viable. The sponsor was advised that if the assay limits at batch release were tightened then a longer shelf life may be possible.

Subsequently, in a letter dated 14 February 2012, the sponsor requested a shelf life of 24 months below 25°C in conjunction with tightened assay limits at batch release.

No further stability data were submitted but the existing 24 month data for three batches have been re-analysed in the context of the newly proposed assay limits. It has been determined by regression analysis that a batch released at the new lower release limit would remain above the lower expiry limit of 92.5% during 24 months' storage at 25°C/60% rh.

On this basis, a shelf life of 24 months below 25°C is approved provided the sponsor submits formally amended finished product release specifications with the tightened assay limits

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

The nonclinical studies were well presented and described. The nonclinical submission contains some older studies from the early 1980s but most of the studies are relatively

recent and Good Laboratory Practice (GLP) compliant. The early non GLP genotoxicity studies in bacteria and yeast have been supplemented with more recent GLP studies. The pharmacokinetic data are limited because of the low level of absorption of rifaximin in the GI tract. Similarly, toxicokinetics are not available for all of the toxicity studies because of the low levels of systemic rifaximin resulting from the low level of absorption.

Pharmacology

Primary Pharmacodynamics

Mechanism of action

Rifaximin, like other rifamycins, is a specific inhibitor of RNA synthesis in microorganisms. There is also some evidence from *in vitro* studies that rifaximin may reduce bacterial colonisation by reducing adherence to epithelial cells, however, this effect may be specific to particular bacteria. Another *in vitro* study suggested that rifaximin may also reduce inflammatory cytokine release. Pathogens isolated from patients with traveller's diarrhoea had reduced expression of virulence factors (enterotoxins, surface adhesion factors and matrix metalloproteinase-9) in the presence of rifaximin.

The mechanism of action of rifaximin in hepatic encephalopathy is uncertain. Hepatic encephalopathy is a reversible deterioration in neurologic function associated with liver failure and portosystemic venous shunting. The brain is thereby exposed to nitrogenous substances derived from the GI tract (notably ammonia), which are normally detoxified by the liver. It is thought that a local action on the intestinal microbial flora affects ammonia absorption from the intestine; systemic ammonia may contribute to the neurological syndrome of hepatic encephalopathy in hepatically dysfunctional patients with reduced ability to detoxify ammonia in the portal circulation.

In vitro studies

Rifaximin was active *in vitro* against a broad range of bacteria and was comparable to both rifampicin and neomycin. Rifaximin was not active against yeasts, viruses or parasites. Rifaximin activity against important anaerobic bacteria of faecal flora was comparable to that of rifampicin. Antibacterial activity against enteropathogens producing traveller's diarrhoea was considered to be intermediate compared with other antimicrobials. The minimum inhibitory concentration (MIC) against *Vibrio cholera* was 0.5-2 µg/mL compared with 0.5-64 µg/mL for tetracycline. Rifaximin activity against *Helicobacter pylori* was comparable to rifampicin and no potentiation between rifaximin and other compounds was noted. Resistance development to rifaximin (via a chromosome-mediated mechanism) was examined against several aerobic and anaerobic bacterial strains; the degree of resistance was similar to rifampicin. Rifaximin also did not produce an increase in resistance in rifampicin-resistant enterococcus from patients with travellers' diarrhoea. In patients with ulcerative colitis, there was no effect of rifaximin (600 mg three times a day (td) for ten days) on the microbial equilibrium or the selection of resistant strains. Overall, the available data indicate that rifaximin is as effective as other compounds and does not produce a higher level of resistance than other compounds.

In vivo studies

Rifaximin at 1 mg/kg/day in rats inhibited most aerobic species and total anaerobic cocci, compared to a similar effect by rifampicin at 30 mg/kg/day. A similar analysis of the faecal flora following 30 mg/kg/day of rifaximin or neomycin showed inhibitory effects of rifaximin on both total aerobes and Salmonellae, while neomycin only affected Salmonellae. In *Staphylococcus*-infected mice, oral rifaximin did not protect against

mortality, while rifampicin was protective with an 50% effective dose (ED₅₀) of 0.15 mg/kg, reflecting the low GI absorption of rifaximin.

Secondary Pharmacodynamics

Rifaximin was tested for its activity *in vitro* against different strains of *Mycobacterium tuberculosis* isolated from pulmonary and renal tuberculosis patients and its ability to produce cross-resistance to rifampicin, which is used against this mycobacterium. At concentrations up to 270 ng/mL there were similar MIC values for rifaximin and rifampicin indicating no selection of resistant pathogens by rifaximin. This is consistent with the low absorption of rifaximin from the GI tract. This concentration is ≥ 13 times the clinical exposure based on the peak plasma concentration (C_{max}). In an *in vivo* study in *Mycobacterium tuberculosis*-infected guinea pigs, rifampicin at 30 mg/kg completely prevented tuberculous infection after 90 days, while rifaximin at 60 mg/kg had no effect. The data, supported by expert opinions, indicate that rifaximin does not enhance cross-resistance to rifampicin.

In mice with induced acute colitis, rifaximin was found to reduce the level of inflammation and increase survival. It is proposed that the reduction in the level of colon bacteria may be linked to the reduction in colitis severity, possibly by preventing immune system activation.

Safety pharmacology

The focus of the safety pharmacology studies was on GI effects in mice and rats, given the poor absorption of rifaximin in the GI tract; however, studies on potential effects on the CNS, cardiovascular system, respiratory system and renal function were also undertaken. *In vivo* studies were conducted at dose levels up to 1000 mg/kg, equivalent to 4 to 8 times the maximum recommended human dose (MRHD) on a mg/m² basis. At this dose level, there were no significant effects on heart rate, blood pressure, respiratory parameters, spontaneous motor activity or behaviour, although there was an increase in electrolyte excretion and a prolongation of hexobarbitone-induced sleeping time. No treatment related effects were seen at 300 mg/kg. A potential to induce a QT interval² prolongation could only be assessed *in vitro* in the hERG assay and the 50% inhibitory concentration (IC₅₀) was >100 μ M (equivalent to approximately 3700 times the clinical peak plasma concentration (C_{max}) in hepatically impaired patients). In relation to potential GI effects, there was no significant effect on gastric motility in mice or any evidence of GI damage in rats after oral administration at 1000 mg/kg. Gastric secretion was also not affected in rats by intraduodenal administration at 1000 mg/kg. Overall, no adverse effects were identified at clinically relevant exposure levels.

Pharmacodynamic drug interactions

The potential for rifaximin to influence the diazepam-induced protection of mice from metrezol-induced convulsions was examined. Unlike rifampicin, rifaximin did not induce the metabolism of the anticonvulsant diazepam at 1000 mg/kg.

² QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

Pharmacokinetics

Nonclinical pharmacokinetic studies were conducted in the mouse, rat, rabbit and dog to support the pharmacology and toxicity studies.

Single dose studies in rats and dogs demonstrated very low absorption of rifaximin following oral administration. In rats administered ^{14}C -rifaximin, low levels could be detected in the serum in the first hr of dosing only, with a maximum level at 15-30 min. The absorption was estimated to be $\leq 2\%$ of the oral dose. In dogs administered ^{14}C -rifaximin, maximum levels were measured at 1-2 h and the absorption was estimated to be 0.5% of the administered dose. Volume of distribution and clearance could not be determined and absolute bioavailability and potential for biliary excretion have not been investigated. Further studies in dogs demonstrated the low exposure of the commercial α polymorphic form of rifaximin compared to the γ polymorphic form (approximately 70 fold, based on AUC)³.

Following repeated exposure, C_{max} and AUC did not increase with dose in males whereas both values increased slightly in females. In rats, C_{max} and AUC increased in a much less than dose proportional manner but there was no evidence of accumulation. In dogs, C_{max} and AUC increased in a much less than dose proportional manner up to 300 mg/kg/day but there was no evidence of accumulation.

Plasma protein binding was not examined in animal species but human studies indicated that binding to plasma protein was moderate in both healthy subjects (68%) and hepatically impaired subjects (62%). Autoradiographic examination of tissue distribution showed high levels of radioactivity in the GI tract with low levels in the kidney, liver and urinary bladder. There was no evidence of accumulation in melanised tissues.

The metabolism of rifaximin was examined *in vitro* in hepatocytes from rat, rabbit, dog and humans. The major component after 24 h incubation was unchanged rifaximin in all species, with up to 24 other components showing high interspecies variability. The major human metabolite identified *in vitro*, 25-desacetyl-rifaximin (~7%), was a minor metabolite in rabbits and dogs and it was not detected in rats. There were no specific *in vivo* studies to examine metabolism due to the limited absorption of rifaximin. Human mass balance studies ^{14}C -rifaximin oral (PO) showed that of the 96.94% recovery, 96.62% of administered tracer was recovered in faeces as unchanged rifaximin and 0.32% was recovered in urine mostly as metabolites, indicating that rifaximin is metabolised following absorption but not by the gut microflora (Study no. RFPK9801). The human metabolite 25-desacetyl-rifaximin was $< 1\%$ of the administered dose. Although exposure to 25-desacetyl-rifaximin was limited in the nonclinical toxicity studies, the very low GI absorption of rifaximin and consequent minimal systemic exposure to this metabolite under *in vivo* conditions allays concerns regarding its potential toxicity. Cytochrome P450, specifically cytochrome CYP3A4, was shown to be involved in rifaximin metabolism following incubation with human microsomes.

Pharmacokinetic drug interactions

The potential for rifaximin to inhibit or induce CYP450 isozymes was tested *in vitro*. Inhibition occurred only at a high concentration ($\text{IC}_{50} = 25 \mu\text{M}$, equivalent to approximately 900 times the clinical C_{max} in hepatically impaired patients). No induction of

³ The potential for conversion of the α polymorphic form to other polymorphic forms during manufacture and storage was raised with the sponsor (S31), since systemic exposure may be much greater with forms such as the γ polymorphic form. The sponsor has advised that such interconversion has not been observed with either API or product.

CYP450 was noted 5 μM (equivalent to approximately 180 times the clinical C_{max} in hepatically impaired patients), while rifampicin induced CYP450 at 0.2 μM and above.

In vitro studies in Caco-2 cells show that the partial transportation of rifaximin by this system was linear up to 50 μM . There was also no inhibition of digoxin transportation at 50 μM rifaximin. Rifaximin could inhibit other transporters, MDR1, MRP2, MRP4 and BCRP with IC_{50} values of 2 μM , 4.5 μM , 35.8 μM and 108 μM , respectively (equivalent to >75 times the clinical exposure based on C_{max}). Inhibition of the human bile export pump (BSEP) by rifaximin occurred with an IC_{50} value of 83 μM (equivalent to >3000 times the clinical C_{max} in hepatically impaired patients). The available data do not indicate a potential for rifaximin at therapeutic exposures to negatively interact with other drugs as a result of its pharmacokinetic activity.

Relative exposure

The systemic oral bioavailability of rifaximin is very low in all species studied. Since systemic exposure is not required for the pharmacological activity of rifaximin, measurement of systemic exposure is only an indirect measure of relative exposure in the GI tract. The systemic exposure has been studied in a number of clinical trials. Exposure ratios have been calculated based on animal/human AUC_{tau} , steady state) and C_{max} values from human studies in healthy volunteers administered rifaximin 550 mg twice daily. Exposure ratios for the repeat dose studies have also been calculated relative to hepatically impaired patients.

Table 4. Repeat dose toxicity studies; exposure relative to healthy volunteers

Species	Study duration (weeks)	Dose mg/kg/day	C_{max} ng/mL (m/f)	C_{max} Exposure ratio ^a	$\text{AUC}_{0-24 \text{ h}}$ ng.h/mL (m/f) ^c	AUC Exposure ratio ^a
Repeat dose toxicity studies						
Mouse	28 days	250	10.2/15.0	3/4.4	95.9/117	7.8/9.5
		1000	9.78/13.1	3/3.8	69.9/176	5.7/14.3
		2000	11.8/25.8	3.5/7.5	88.4/215	7.2/17.5
Rat	Day 1 of 26 week	5	14.21	4.2	50.65	4.1
	study ^b	150	20.83	6.1	92.35	7.5
		300	25.04	7.3	126.7	10.3
Dog	39 week	100	16.97	5.0	61.35	5.0
		300	21.82	6.4	75.45	6.1
		1000	21.88	6.4	105.7	8.6

Species	Study duration (weeks)	Dose mg/kg/day	C _{max} ng/mL (m/f)	C _{max} Exposure ratio ^a	AUC _{0-24 h} ng.h/mL (m/f) ^c	AUC Exposure ratio ^a
Repeat dose toxicity studies						
Dog	4 week	1000	7/10	2/3	80/113	6.5/9.2
		300 (amorp.) ^d	1923/1445	564/424	8750/9292	711/755
		1000 (amorp.)	2922/2226	857/653	12423/7155	1010/581

^a Exposure ratio based on human study with healthy volunteers (550 mg twice daily: C_{max} 3.41 ng/mL; AUC_{tau} 12.3 ng.h/mL (Study no. RFPK 1007).

^b AUC could not be determined at 26 weeks as the concentration of rifaximin was too low.

^c AUC_{0-24h} is compared with AUC_{tau} (area under the curve from pre-dosing to the end of the treatment period, namely 12 h). Given the rapid excretion of rifaximin, these AUC measurements are comparable).

^d amorphous form rifaximin.

Table 5. Repeat dose toxicity studies; exposure relative to hepatically impaired patients

Species	Study duration (weeks)	Dose mg/kg/day	C _{max} ng/mL (m/f)	C _{max} Exposure ratio ^a	AUC _{0-24 h} ng.h/mL (m/f)	AUC Exposure ratio ^a
Repeat dose toxicity studies						
Mouse	28 days	250	10.2/15.0	0.5/0.7	95.9/117	0.7/0.9
		1000	9.78/13.1	0.5/0.6	69.9/176	0.5/1.3
		2000	11.8/25.8	0.6/1.2	88.4/215	0.7/1.6
Rat	Day 1 of 26	5	14.21	0.7	50.65	0.4
	week study	150	20.83	1.0	92.35	0.7
		300	25.04	1.2	126.7	1.0
Dog	39 week	100	16.97	0.8	61.35	0.5

Species	Study duration (weeks)	Dose mg/kg/day	C _{max} ng/mL (m/f)	C _{max} Exposure ratio ^a	AUC _{0-24 h} ng.h/mL (m/f)	AUC Exposure ratio ^a
Repeat dose toxicity studies						
		300	21.82	1.0	75.45	0.6
		1000	21.88	1.0	105.7	0.8
Dog	4 week	1000	7/10	0.3/0.5	80/113	0.6/0.9
		300 (amorp.)	1923/1445	91/68	8750/9292	67/71
		1000 (amorp.)	2922/2226	138/105	12423/7155	95/55

^a Exposure ratio based on human study with hepatically impaired patients (550 mg twice daily: C_{max} 21.1 ng/mL; AUC_{tau} 130 ng.h/mL (Study no. RFHE 3002PK).

Table 6. Embryofetal development; exposure relative to healthy volunteers

Species	Study	Dose mg/kg/day PO (gavage)	C _{max} ng/mL ^b	C _{max} Exposure ratio ^a	AUC _{0-24 h} ng.h/mL	AUC Exposure ratio ^a
Rabbit	Embryofetal toxicity (AFW/09/973155); PO)	62.5	ND	-	ND	-
		250	1.7	0.5	8.3	0.7
		1000	4.0	1.2	17.0	1.4

^a Exposure ratio based on human study (550 mg twice daily: C_{max} 3.41 ng/mL; AUC_{tau} 12.3 ng.h/mL (Study no. RFPK 1007).

Toxicology

Acute toxicity

Rifaximin demonstrated low acute toxicity in studies conducted in mice and rats. Piloerection was the only clinical sign of toxicity. Discoloured faeces were observed as result of the high level of excretion of rifaximin. The effects observed in the IV studies (hunched posture, respiratory distress) were probably due to the vehicle formulation of 50% polyethylene glycol 400 (PEG 400). The minimum nonlethal dose in mice and rats was >2000 mg/kg by the oral route.

Repeat dose systemic toxicity

Repeat dose toxicity with rifaximin was examined in mice (up to 4 weeks), rats (up to 26 weeks) and dogs (up to 39 weeks).

In mice after oral administration up to 2000 mg/kg/day, there was no effect on bodyweight gain and only slight clinical pathology changes which were not clearly treatment related. Histopathology was normal and no target organ could be identified. The NOAEL was 2000 mg/kg/day (approximately 12 times the clinical exposure for healthy volunteers, and similar to clinical exposure for hepatically impaired patients, based on AUC).

In rats after oral administration, there was reduced bodyweight gain and non-specific toxicity at 300 mg/kg/day after one month. After 26 weeks, bodyweight reduction was evident in males at 50 mg/kg/day and in males and females at 150 mg/kg/day but these bodyweight changes were fully reversible after 4 weeks. The non dose related lymphocyte changes were not accompanied by any other evidence of immunotoxicity and may be stress related. The observed changes are considered to be secondary to the effects of rifaximin on the intestinal microflora. This is supported by the more recent 4 week study at 1000 mg/kg/day. The NOAEL was 300 mg/kg/day (10 times the clinical exposure for healthy volunteers and similar to clinical exposure for hepatically impaired patients, based on AUC).

In dogs after oral administration (39 weeks), there was a slightly reduced bodyweight gain at 1000 mg/kg/day together with reduced thymus weight. There was evidence of atrophy at all dose levels but after the recovery period this was evident in only one high dose (HD) dog (1000 mg/kg/day). Reduced thymus weight is common to all broad-spectrum non absorbable antibiotics at high dose levels⁴. The No observable adverse effect level (NOAEL) was 300 mg/kg/day (6 times the clinical exposure for healthy volunteers and about half the clinical exposure for hepatically impaired patients, based on AUC).

Overall, the majority of the observed effects can be linked with the rifaximin-induced effects on the intestinal microflora. Longer term toxicity studies were not considered necessary, given the low absorption of rifaximin and results of the shorter term studies. However, the exposure margins achieved in the key repeat dose toxicity studies are only modest with regard to hepatically impaired patients (similar to or below clinical exposure), who represent the most valid human comparator group, given the indication. With the relatively benign toxicity profile, an investigation of the effects of greater exposure in test species was probably feasible; possibly using a different administration route such as IV in order to better define any target organ toxicity at several multiples of clinical exposure in hepatically impaired patients. This concern was also noted in the nonclinical evaluation report on rifaximin by the FDA⁵, which stated that the sponsor should undertake a chronic oral toxicology study with systemic (AUC) exposure comparable with that observed in cirrhotic patients.

⁴ Van Der Waaij D. (1986) The influence of intestinal microflora on the relative thymus weight. *Med. Microbiol. Immunol.* 175 335-340.

⁵ This report also noted that several earlier non-GLP repeat dose studies in rats and dogs (not included in the current dossier) found evidence of hepatotoxicity (hepatic steatosis, hepatomegaly, infiltrate into/mild degeneration in liver parenchyma, centrilobular fatty degeneration in the liver) at PO doses lower than those in the current GLP studies. The reasons for this discrepancy are not known, but may result from greater drug absorption in the pre-GLP studies due to a difference in the administered formulation.

Genotoxicity and carcinogenicity

The genotoxic potential of rifaximin was examined in *in vitro* studies in bacteria, yeast and mammalian cells and *in vivo* studies in rats. In *Salmonella typhimurium* strains TA97, TA100, TA1535 and TA1538, there was no evidence of an increased frequency of mutations at 5000 µg/plate. In *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae* D4, there was no evidence of an increased frequency of mutations at 1000 µg/plate. In Chinese hamster ovary cells there was no evidence of an increase in the frequency of mutations at 1000 µg/mL. In human lymphocytes, there was no evidence of an increase in the number of cells with chromosome aberrations at 100 µg/mL. In the rat micronucleus test, there was no increase in the incidence of micronucleated polychromatic erythrocytes at 2000 mg/kg PO (approximately 16 times the MRHD, based on body surface area). There was no increase in unscheduled DNA synthesis in rat hepatocytes isolated from rats 2 h or 14 h after *in vivo* treatment at 2000 mg/kg. The overall conclusion is that rifaximin does not have genotoxicity potential *in vitro* or *in vivo*. Although the metabolite 25-desacetyl-rifaximin was not detected in rats, exposure to this metabolite under *in vivo* conditions would be very low (see *Pharmacokinetics* above).

The potential for carcinogenicity was examined in a long term (2 year) oral study in Sprague Dawley (SD) rats and a short term (26-week) study in TG.rasH2 transgenic mice. In the 2 year study, rats were administered rifaximin up to 250 mg/kg/day by oral gavage. There were no clinical or macroscopic signs of toxicity. Microscopic examination did not reveal any evidence of an increased tumour incidence except for a non significant increased trend in malignant schwannomas in the heart of males but not females. These tumours are reported to occur sporadically in rats (up to 1.0%⁶) and were reported to be present in historical controls (up to 1.7%). The apparent dose-response relationship and the HD incidence (5%) clearly exceeding the historical control values suggests a possible relationship to treatment. Toxicokinetics were not examined but exposure at the HD was estimated to be approximately 2 times the clinical exposure, based on a mg/m² dose comparison. In the TG.rasH2 transgenic mice, there was no significant dose related or treatment related increase in the spleen and lung tumours induced by the positive control. The positive controls produced a high incidence of spleen and lung tumours. The rifaximin mean plasma concentration at the HD of 1500/2000 mg/kg/day (m/f) at 26 weeks was 4 times (m) or 2 times (f) the clinical (C_{max}) exposure in healthy volunteers but less than clinical exposure in hepatically impaired patients. Overall, although there was no unequivocal evidence of carcinogenic liability following rifaximin treatment, there were interpretative limitations with the available data. The schwannoma result in rats is recommended for inclusion in the PI.

Reproductive toxicity

Fertility, embryofetal development and pre and post natal development were examined in rats. Embryofetal development was also examined in rabbits. There were no specific studies examining placental transfer or excretion into milk, indicating that caution may be warranted if rifaximin is used during pregnancy or breast-feeding; however, given the minimal systemic absorption of rifaximin both of these would be expected to be very low. In rats, there was no effect of rifaximin on fertility at PO doses up to 300 mg/kg/day, although bodyweight gain in pregnant females was decreased during early gestation but not during lactation (likely to be related to the antimicrobial effect of rifaximin on

⁶ Novilla M, Sandusky G, Hoover D, Ray S, Wightman K (1991) A retrospective survey of endocardial proliferative lesions in rats. *Vet. Pathol.* 28 156-165.

intestinal microflora). When dosing was continued through the period of organogenesis, there was no treatment related effect on visceral or skeletal abnormalities. In a pre/postnatal development study in rats, there was a slight decrease in bodyweight gain at 150 and 300 mg/kg/day in the F₀ generation⁷ during gestation but not during lactation. This did not affect reproductive performance or development in subsequent generations. Toxicokinetic measurements were not carried out in these rat studies but the reproductive NOAEL of 300 mg/kg/day established in all studies was approximately 2.5 times the MRHD, based on body surface area.

In rabbits treated during the period of organogenesis there was a decrease in bodyweight gain during the initial treatment period, consistent with the effect of rifaximin on gut microflora and the significant nutritional dependence of rabbits on the activity of the gut microflora. This effect is also considered to be responsible for the increased incidence of skeletal anomalies in treated animals. There was no evidence of teratogenicity related to rifaximin treatment. The systemic exposure (AUC) measured in does at the NOAEL of 1000 mg/kg/day is slightly greater (1.4 times) than anticipated clinical exposure in healthy volunteers but less than clinical exposure in hepatically impaired patients.

Pregnancy classification

The available studies in rats and rabbits provide adequate evidence that oral rifaximin is not teratogenic. There is only weak evidence of fetal toxicity which is likely to be secondary to the pharmacological effects of rifaximin. While the available kinetic data to determine the potential fetal exposure was limited, there are adequate data available elsewhere to demonstrate that systemic exposure is very low and therefore fetal exposure would also be very low. On the basis of the nonclinical data, a Pregnancy Category B1⁸ classification is justified.

Use in children

There were no studies examining effects in juvenile animals as rifaximin is proposed for use in adults only. Rifaximin is not intended for use in children.

Immunotoxicity and other studies

A 4 week immunotoxicity study in rats was undertaken to examine further the effects observed on lymphatic tissues in the repeat dose studies in rat and dog. Following oral administration up to 500 mg/kg/day for 4 weeks, there was no increase in plaque-forming cells to sheep white blood cells, indicating an absence of a humoral antibody response; achieved systemic exposure was 3.5 times the clinical C_{max} in healthy volunteers and about half the clinical C_{max} in hepatically impaired patients. There were also no changes observed in lymphatic tissues. Based on these data, rifaximin is not considered to have any immunotoxicity potential.

In a study conducted to compare the liver toxicity of rifaximin α with amorphous rifaximin, there was no evidence of toxicity related to amorphous rifaximin following systemic exposure to amorphous rifaximin which is approximately 800 times the clinical

⁷ The initial parent generation in a multi-generation reproduction study.

⁸ Category B1=Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

exposure based on C_{max} and AUC, and systemic exposure to rifaximin α which is 2.5 and 8 times the clinical exposure based on C_{max} and AUC, respectively.

Impurities

The potential impurities derived from the synthetic route include 2-amino-4-methylpyridine (Impurity A) and several rifaximin-related impurities and an *in silico* QSAR modelling analysis [OECD (Q)SAR Application Toolbox] showed that only 2-amino-4-methylpyridine had the potential to interact with DNA. The impurities rifamycin B (Impurity B), rifamycin SV (Impurity C), rifaximin Y (Impurity D), rifamycin S (Impurity E), rifamycin O (Impurity F), oxidised rifaximin (Impurity G) and hydroxy-rifaximin (Impurity H), and rifaximin *per se*, did not possess any alerts for potential DNA binding. In *Salmonella typhimurium* strains TA97, TA100, TA1535 and TA1537 or in *Escherichia coli* WP2, there was no evidence that 2-amino-4-methylpyridine increased the mutation frequency at 5000 $\mu\text{g}/\text{plate}$. This finding confirmed earlier literature reports that 2-amino-4-methylpyridine was negative in Salmonella mutagenicity assays in the presence of norharman (a comutagen), in the presence and absence of metabolic activation⁹. No further genotoxicity testing of 2-amino-4-methylpyridine, or any further studies of the other abovementioned impurities, is considered necessary¹⁰.

Any rifaximin-related impurities which are orally bioavailable have the potential to be metabolised. Simulated metabolism of these impurities (GI, liver, skin and microbial metabolites) indicated a number of potential metabolites with structural alerts for potential DNA binding. Based on the low oral rifaximin bioavailability, it is likely that any systemic exposure of these impurities would be very low, with levels of any (theoretical) metabolites even lower. The risk of genotoxicity from potential exposure to these compounds is considered very unlikely.

For the impurity rifaximin Y (sum of rifaximin impurities rifaximin D and H, which co-elute in the test method), a specification of no more than (NMT) 0.5% is sought for the API. Because of the low quantities available, the genotoxicity of rifaximin Y was assessed with rifaximin spiked with 0.6% rifaximin Y (permitted in guidelines¹¹). In L5178Y mouse lymphoma cells¹², there was no evidence that this mixture increased the mutation frequency. At the rifaximin MRHD of 550 mg twice daily (22 mg/kg/day in a 50 kg individual), the maximum daily intake of rifaximin Y would be $22 \times 0.5\% = 0.11 \text{ mg/kg/day} = 3.63 \text{ mg/m}^2/\text{day}$, if present at 0.5%. This exposure to rifaximin Y was exceeded at the high doses in the 26 week rat and 39 week dog repeat dose toxicity studies in which rifaximin Y was present in the administered batches at 0.23-0.27% (rat: $0.81 \text{ mg/kg/day} = 4.86 \text{ mg/m}^2/\text{day}$; dog: $2.7 \text{ mg/kg/day} = 54 \text{ mg/m}^2/\text{day}$).

The proposed specification for rifaximin Y of NMT 0.6% in the API was considered qualified.

⁹ Wakabayashi K, Yahagi T, Nagao M, Sugimura T (1982) Comutagenic effect of norharman with aminopyridine derivatives. *Mutation Research*, 105, 205-210; Sugimura T, Nagao M, Wakabayashi K (1982) Metabolic aspects of the comutagenic action of norharman. In: R Snyder, DV Parke, J Kocsis, DJ Jollow, GG Gibson (Eds) *Biological Reactive Intermediates 2: Chemical Mechanisms and Biological Effects*, Plenum, NY.

¹⁰ EMA/CHMP/SWP/431994/2007 Rev. 3: Questions and answers on the 'Guideline on the limits of genotoxic impurities'

¹¹ Q3B(R2) *Note for Guidance on Impurities in New Drug Products* (CPMP/ICH/2738/99).

¹² For an antibiotic, considered a more appropriate assay than a bacterial reverse mutation assay.

Benefit-risk assessment***Assessment of benefits:***

- Based on the pharmacology data, rifaximin is active against a broad range of GI bacteria. While it is an inhibitor of RNA synthesis, the mechanism of its effectiveness may also involve other factors.
- Development of resistance to rifaximin is low because of the high concentrations in the GI tract and rifaximin does not enhance cross-resistance to rifampicin against *Mycobacterium tuberculosis*.
- There was no evidence of treatment-related effects on CNS, cardiovascular, respiratory or renal functions or gastric motility/secretion, nor evidence of GI damage at estimated exposures higher than clinical exposure.
- There was no evidence of pharmacodynamic or pharmacokinetic drug interactions.
- There was little/no evidence of systemic toxicity, genotoxicity, reproductive or other toxicity.

Assessment of risks:

- There is no direct evidence from the nonclinical data that rifaximin will provide the benefits claimed in relation to the indication as there are no suitable animal models of hepatic encephalopathy.
- Exposure to rifaximin is approximately 10 times higher in hepatically impaired patients than in healthy volunteers and animal studies did not reach exposure levels that provided an adequate exposure margin. An appropriate postmarketing nonclinical study is recommended to address this.
- An uncommon carcinogenicity finding in rats (malignant schwannomas) could not be dismissed.
- Given the much greater oral bioavailability of other polymorphic forms, there is a need to ensure that the commercial preparation of rifaximin is the poorly-absorbed polymorphic form, rifaximin α .

Nonclinical summary and conclusions

- The sponsor has provided studies to examine the pharmacodynamics, pharmacokinetics and toxicity of rifaximin. Most of the studies are relatively recent and are GLP-compliant. The kinetic data are limited because of the low levels of GI absorption.
- Primary pharmacodynamics studies were conducted both *in vitro* and *in vivo*. The *in vitro* studies confirmed the high activity of rifaximin against a range of anaerobic bacteria of the faecal flora, as well as against enteropathogens producing 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 well below the clinical exposure.
- Secondary pharmacology studies confirmed that rifaximin does not enhance cross-resistance to rifampicin against *Mycobacterium tuberculosis*. Safety pharmacology studies confirmed that rifaximin has no adverse effects on the CNS, cardiovascular system, respiratory system or renal function at estimated exposures several times the clinical exposure. *In vitro*, there was no potential to induce QT interval prolongation at

concentrations several orders of magnitude the clinical exposure. *In vivo* studies were not possible due to the low absorption. There was also no effect of rifaximin on gastric motility/secretion, no evidence of GI damage at these exposure levels and no evidence that rifaximin induced the metabolism of diazepam.

- Pharmacokinetics was examined in mouse, rat, rabbit and dog. In all species, there was a very low absorption of rifaximin following oral administration ($\leq 2\%$ in rats and 0.5% in dogs), with $<1\%$ of the dose excreted in the urine. Maximum serum concentrations were seen in 1-2 h. A comparative study in dogs demonstrated the low absorption of the α polymorphic form compared to other forms. After repeated exposure, C_{max} and AUC values increase in a much less than dose proportional manner, with no evidence of accumulation. Plasma protein binding of rifaximin was moderate (68%). Autoradiography demonstrated the low absorption of rifaximin with high levels of radioactivity in the GI tract and very low levels in kidney, liver and urinary bladder. The absorbed rifaximin was metabolised significantly with up to 24 components identified. The major (*in vitro*) metabolite in humans was 25-desacetyl-rifaximin ($\sim 7\%$), a minor metabolite in other species. Rifaximin did not induce or inhibit cytochrome P450, but CYP3A4 is involved in rifaximin metabolism. There was no evidence of rifaximin affecting efflux proteins at clinically relevant doses.
- The general toxicity of rifaximin was examined after single and repeated exposure in mice, rats and dogs. Acute toxicity was very low with signs of toxicity attributed to the vehicle only. After repeat dose exposure, there was no clear treatment related toxicity in mice, rats showed reduced bodyweight and non specific toxicity at 300 mg/kg/day (fully reversible), and in dogs there was reduced bodyweight and thymus weight at 1000 mg/kg/day. Generally, no clear treatment related or target organ toxicity was apparent; observed effects in all species may be linked to the effects of rifaximin on intestinal microflora. Achieved systemic exposures (AUC) were 6-12 times the clinical exposure in healthy volunteers but similar to or less than clinical exposure in hepatically impaired patients. There was no evidence of immunotoxicity in a 4 week rat study at modest exposure.
- There was no evidence of genotoxicity in *in vitro* studies in bacteria, yeast and mammalian cells or in an *in vivo* micronucleus study in rats. A 2 year oral carcinogenicity study in rats was unremarkable apart from a non significant increased trend in males of malignant schwannomas in the heart at a HD incidence (5%) exceeding historical control (1.7%) (exposure estimated to be 2 times the clinical exposure). There was no evidence of carcinogenicity in a 6 month oral study in transgenic mice at plasma exposures 2 to 4 times the clinical C_{max} in healthy volunteers but less than C_{max} in hepatically impaired patients.
- Specific studies on placental transfer or excretion into milk were not undertaken but both are expected to be very low. Effects on fertility and pre/postnatal development in rats and on embryofetal development in rats and rabbits were unremarkable, the decreased bodyweight gain in both species and the skeletal anomalies in rabbits likely secondary to the effect of rifaximin on gut microflora. Estimated exposures in rats were 2.5 times the clinical exposure, while rabbit exposure was approximately 1.5 times the clinical exposure (healthy volunteers) but less than clinical exposure in hepatically impaired patients.
- Of the known rifaximin impurities, QSAR modelling showed that only 2-amino-4-methylpyridine had the potential to interact with DNA but bacterial mutation studies with this compound were negative. Rifaximin Y is qualified at the sought specification of NMT 0.5%.

Conclusions and recommendations

Nonclinical evidence for efficacy

The nonclinical *in vitro* and *in vivo* data provide adequate evidence that rifaximin is active against a broad range of GI bacteria. In this regard it is likely that it can assist in the treatment of hepatic encephalopathy. This cannot be assessed from the nonclinical data and the assessment of its efficacy will depend on clinical studies.

Toxicological findings impacting on safety

Overall, the nonclinical studies provide little evidence of potential adverse effects associated with rifaximin and it is likely that the few observed effects are secondary to the effect on the intestinal microflora. The benign toxicity profile refers to the poorly absorbed rifaximin α polymorphic form, which is the form proposed for manufacture, with apparently no propensity for interconversion. The main toxicological issue is the very modest exposures achieved in the animal studies compared to the clinical exposure in hepatically impaired patients (the most valid comparator group). A secondary issue was the apparent hepatotoxicity reported in earlier non-GLP repeat dose toxicity studies in rats and dogs, not reproduced at higher doses in the current GLP studies. These concerns have prompted the FDA to require the postmarketing conduct of a chronic oral nonclinical toxicology study, with achieved AUC exposures comparable to the highest AUCs observed in cirrhotic patients. This study report is scheduled for submission to the FDA by 30 June 2013.

Thus, although the nonclinical concerns did not warrant objection to registration as proposed by the sponsor, it was recommended that the report from the chronic oral nonclinical toxicology study also be submitted to the TGA, as a condition of registration.

Benefit/risk conclusion

On the basis of the nonclinical data, the potential benefits of rifaximin outweigh the risks. The clinical data will provide further clarification in relation to the efficacy of rifaximin.

IV. Clinical findings

Introduction

The key body of data in support of this application consists of 12 primary clinical pharmacology studies provide PK data for this marketing application (MA) for RFX for prevention of recurrence of HE. Five studies have investigated the pharmacokinetics (PK) of the 550 mg tablet formulation; 4 in healthy subjects (RFPK1007, RFDI1008, RFDI1009 and RFPK1002) and 1 of these studies in subjects with HE (RFHE3002PK). Seven additional studies (RFPK9901, RFPK1004, RFPK9801, RFHE9702, RFPK1011, RFDI1002, and RFDI1001) provide further PK data for RFX.

The clinical studies in this application (Phase I, II and III) complied with TGA adopted EU guidance¹³, an internationally accepted standard for the design, conduct, recording and reporting of clinical trials.

¹³CPMP/ICH/135/95 Note for guidance on good clinical practice. (Annotated with TGA comments)
www.tga.gov.au/pdf/euguide/ich13595.pdf

Pharmacokinetics

Several different polymorphous forms of RFX, those with minimal systemic absorption (form α) have moved into clinical development, the rationale being the potential therapeutic use of a broad antimicrobial spectrum coupled with minimal intestinal absorption for the treatment of intestinal bacterial infections. Nonclinical PK studies were conducted in 4 animal species (mouse, rat, rabbit and dog).

Methods

Analytical methods

A liquid chromatographic tandem mass spectrometric (LC-MS/MS) bioanalytical assay for the measurement of RFX over the concentration range 1-100 ng/mL has been cross validated with the established and analogous bioanalytical assay for RFX in human plasma in several animal species including dog and rabbit. Standard laboratory analyses of safety bloods; standard electrocardiogram (ECG) and grading of adverse events was used in these PK studies. Standard microbiological culture techniques were utilised to culture faecal pathogens and assess the minimum inhibitory concentrations required to inhibit 50% or 90% of growth of the organism(s), that is, the MIC50 and MIC90 respectively.

Pharmacokinetic data analysis

Individual plasma concentrations for each time point and the derived PK parameters were listed for each subject for each treatment with the caveat that this antibiotic has very low systemic bioavailability and hence plasma levels could not reliably be detected in several of the PK studies. PK parameters including AUC and C_{max} were log transformed using a one way analysis of variance (ANOVA) model.

Statistical analysis

Safety: Demographics were summarised in the larger studies. Tabulated variables included adverse events (AE), clinical laboratory tests and vital signs. Summary statistics, including the mean, standard deviation and coefficient of variation were provided for each treatment. *PK:* Where applicable and where possible (due to the low systemic absorption of RFX), repeated measure analyses of variance model, extracting effects due to treatment, sequence, period and subject were fit. Point estimates of the mean difference between the treatments and the reference treatment(s) were calculated. 90% confidence intervals were provided where applicable.

Absorption

RFX has extremely poor oral absorption and systemic exposure of RFX given orally is very low regardless of dose, disease state or feeding state. In a Caco-2 cell model, RFX showed very low apical to basolateral permeability (*PK0903*). Following a single 400 mg oral dose in fasted and fed healthy subjects, mean AUC values were 18.4 ng.h/mL and 34.7 ng.h/mL, respectively (*RFPK9901*). Administration of a single 550 mg oral dose to fasted and fed healthy subjects resulted in mean AUC values of 11.1 ng.h/mL and 22.5 ng.h/mL, respectively (*RFPK1007*). In subjects with liver impairment, systemic exposure was higher versus healthy subjects but still very low. Following repeat dosing of a 550 mg twice daily (bd) regimen in liver-impaired subjects, mean steady-state AUC_{0-t} values of 113 ng.h/mL

and 156 ng.h/mL were observed in Child-Pugh A and Child-Pugh B¹⁴ subjects, respectively (*RFHE3002PK*) representing 10, 13 and 20 fold higher AUC_τ levels versus healthy controls for those with Child-Pugh A, B and C.

Following a single 400 mg ¹⁴C-RFX dose in healthy subjects, >96% of total radioactivity was present in the faeces (*RFPK9801*).

Bioequivalence

There is no IV formulation of RFX, only an oral formulation. The activity of RFX is intended at the luminal level of the GI tract, hence could be viewed as a topical agent. Hence as this antibiotic is not intended for systemic action, there is no PK characterisation which compares the systemic availability of the intended form in comparison with IV administration. The Phase I study (*RFPK1001*) explored the commercial RFX formulation, as expected RFX was poorly absorbed with considerable inter-subject inter-variability; <1% of dose was absorbed from the gut; peak plasma concentrations significantly lower with commercial RFX, p=0.004. Time to C_{max} was similar (0.92 ± 0.49 versus 1.14 ± 0.75, p=0.573) whereas the AUC was significantly lower after commercial dose (p=0.008). Moreover, in *RFPK1002* following single 200 mg dose, RFX tablets disintegrated rapidly in the stomach (within 6-23 minutes), moved through the small intestine within 3.82 through 6.25h post dose, and through the colon within 3.94 through 7.28 h post dose. Rate of delivery to the colon were equivalent for the clinical batch 99002 and the commercial batch F0982.001.

Influence of food

In healthy subjects (*RFPK1007*) food delays RFX absorption as measured by mean time to peak plasma concentration from 0.75 to 1.5 hours and increases the drug's systemic exposure after single 550 mg doses by approximately 2 fold (from 11.1 to 22.5 ng.h/mL). This occurs presumably through the delay in gastric emptying and the subsequent release of bile salts which acts to solubilise poorly soluble drugs. These findings are similar to those observed in healthy subjects under fed and fasted conditions after a single oral 400 mg RFX dose (*RFPK9901*), following a single oral dose of 600 mg RFX and multiple daily doses (i.e. at steady state) (*RFPK1011*). Since the absolute systemic bioavailability of RFX is low and the drug works locally in the GI tract, RFX can be given +/- food.

Distribution

Animal PK studies have demonstrated that 80% through 90% of orally administered RFX is concentrated in the gut with < 0.2% in the liver and kidney and <0.01% in other tissues. Results from a scintigraphy study (*RFPK1002*) in healthy subjects confirm that RFX is retained primarily in the GI tract after oral administration. Following a single 200 mg oral dose, the RFX tablet disintegrated rapidly in the stomach (within 6-23 min post dose) and through the colon within 3.94-7.28 hrs post dose. RFX is moderately bound to human plasma proteins with mean PPB ratio 67.5% in healthy subjects and 62% in patients with hepatic impairment (*PK0902*).

¹⁴ The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. Score: Grade A = 5-6 Grade B = 7-9 Grade C = 10-15.

Elimination

No significant plasma accumulation observed following multiple daily doses. Administration of RFX 550 mg as a single dose or as multiple dose twice a day (bd) or td regimens resulted in mean AUC values of 11.1 ng.h/mL ($AUC_{0-\infty}$), 12.3 ng.h/mL (AUC_{τ} , steady state) and 9.3 ng.h/mL (AUC_{τ} , steady-state), respectively (RFPK1007).

Metabolism/Interconversion and Pharmacokinetics of metabolites and Excretion

Following a single 400 mg ^{14}C -RFX dose in healthy subjects, >96% of total radioactivity was present in the faeces as unchanged drug (RFPK9801), 0.32% recovered in urine mostly as metabolites and 0.03% unchanged drug. RFX accounted for 18% of radioactivity in plasma. These data suggest that the small percentage of RFX absorbed undergoes metabolism but the enzymes responsible are unknown. In a separate study, RFX was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of RFX (N2043).

In vitro and *in vivo* studies (see under *Interactions* section) indicate that the risk of clinically significant drug interactions between RFX and CYP3A4 substrates is minimal.

Consequences of possible genetic polymorphism

RFX has very low systemic absorption and genetic polymorphisms are unlikely to impact on systemic levels. See more discussions under *Interactions* below.

Dose proportionality and time dependency

See *Bioavailability* section above including the *Influence of food*. No significant plasma accumulation observed following multiple daily doses. RFX 550 mg as a single dose or multiple dose bd or td regimen in healthy subjects resulted in mean AUC values of 11.1 ng.h/mL ($AUC_{0-\infty}$), 12.3 ng.h/mL (AUC_{τ} , steady-state) and 9.3 ng.h/mL (AUC_{0-t} , steady-state), respectively (RFPK1007).

Intra and inter individual variability

In regards to RFX systemic exposure, the data suggests that inter and intra individual are not clinically relevant as the drug is so poorly absorbed.

Pharmacokinetics in target population

There are differences in the PK profile of the target population (those with varying degrees of hepatic impairment) and these are detailed below, the consequences of these differences are not thought to be clinically meaningful.

Special populations

Children: not applicable; this application is for an adult population >18 years of age.

Elderly: no specific Phase I data is provided in the elderly population.

Gender: no gender differences revealed in Phase I.

Weight: no specific data was provided; Body Mass Index (BMI) of participants in the PK studies was for the most part in the normal range.

Race: no specific data is provided in this regard, there is not expected to be any differences because of the poor systemic absorption.

Impaired renal function: No studies of RFX in those with renal impairment, no dose adjustment predicted due to the very low systemic absorption of the drug.

Impaired hepatic function: In RFPK 1007, mean AUC_{0-t} and C_{max} values in subjects with Child-Pugh score B (161 ng.h/mL and 25.1 ng/mL, respectively) were approximately 36% and 29% higher than those observed in subjects with Child-Pugh score A (118 ng.h/mL and 19.5 ng/mL, respectively). The terminal half life ($t_{1/2}$) of RFX in subjects with Child-Pugh B score was approximately 29% longer than that observed in subjects with Child-Pugh A score (10.5 hr versus 8.12 hr). The PK of RFX were characterised by an inter subject coefficient of variability (CV%) for AUC_{tau} and C_{max} ranging from approximately 50% to 63%. This was in agreement with the variability previously observed in healthy subjects, that is, CV% of 45% to 60%. In subjects with impaired liver function (RFHE3002PK) given RFX 550mg bd, AUC_{tau} at steady-state in subjects with Child-Pugh A and B were approximately 9.6 and 13.1 fold higher, respectively, than in healthy subjects at steady-state (RFPK1007). A positive correlation between baseline alanine aminotransferase (ALT) and maximum plasma concentration (C_{max}) was also observed. The terminal $t_{1/2}$ of RFX was significantly longer (about 2 fold) in HE subjects versus healthy subjects. This higher exposure found in subjects with HE may be due to a reduction in the systemic clearance of the drug perhaps because of portal-systemic shunts. However, despite this finding of increased systemic exposure in this group, systemic bioavailability is still very low and no dosing adjustment should be required in individuals with hepatic impairment especially when these data are coupled with safety data from RFHE3001 and RFHE3002.

In subjects with enteric infection: The PK of RFX 200mg td was studied in 13 healthy subjects who developed diarrhoea/dysentery when challenged with *Shigella flexneri* (RFPK1004). RFX plasma concentrations were low, although highly variable, as shown by large (>40%) percent coefficients of variation on Day 1 and Day 3. No evidence of RFX accumulation following repeated administration for 3 days. The PK parameter estimates from this study were consistent previous observations.

Population PK analysis

No data provided.

Evaluator's overall comments on pharmacokinetics in special populations:

No RFX dose adjustment needed in any of the special populations studied, including those with hepatic impairment, due to the overall poor systemic absorption of the drug.

Interactions

RFX was examined *in vitro* as a substrate or inhibitor of P-gp in a cell culture model of intestinal absorption (Caco-2 cells) (PK0903); the interaction of RFX with P-gp and other efflux transporters was also studied in membrane vesicles (PK1006). Several *in vitro* studies performed to evaluate the metabolic stability of RFX (PK0100 and PK1003) and the potential for drug interactions due to RFX effects on CYP (PK1005, N2246, PK1004, and N2271) and efflux transporters such as P-gp and BSEP (PK1006 and PK0904). Potential QT prolongation¹⁵ effects were investigated *in vitro* using the human ether-à-go-go-related gene (hERG) assay (PD0901). Additionally, plasma protein binding by RFX in healthy

¹⁵ QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

volunteers and in subjects with hepatic impairment was determined in an *ex vivo* study (PK0902).

In vitro pharmacokinetic interactions

In vitro studies

In vitro metabolic stability (PK1001) and reaction phenotyping (PK1003) studies suggest that hepatic metabolism of RFX in humans is mediated by cytochrome P450 (CYP) 3A4. *In vitro* drug interaction studies demonstrated minimal effects of RFX on the induction or inhibition of CYP3A4. RFX at concentrations up to 50 μM did not significantly inhibit CYP 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 (6 β T); for CYP3A4 (10HMDZ), the RFX 50% inhibitory concentration (IC₅₀) was 25 μM (PK1004). No induction of CYP3A4, CYP1A2 and CYP2B6 enzymes by RFX was observed at concentrations up to 5 μM (PK1005) in human hepatocytes. By comparison, dose-dependent induction of CYP3A4 by rifampin was observed at concentrations from 0.005 to 10 μM (PK1005). At concentrations up to 200 ng/mL, RFX did not inhibit the major CYP drug metabolising enzymes in a human liver microsome assay (PK0101); in cultured human hepatocytes, the maximal ability of RFX to induce CYP3A4 activity was approximately half that of prototypical inducer rifampin at equivalent incubation concentrations (10 μM) (PK0102). No time-dependent inhibition of CYP enzymes was observed *in vitro*; *in vivo* data is presented below.

P-glycoprotein

In vitro study data suggest that RFX is a substrate for P-glycoprotein (P-gp) and potentially for other efflux transport proteins; its substrate status likely contributes to its minimal systemic exposure following oral administration. RFX appears to be a weak inhibitor of P-gp (PK0903) at high molar concentrations (50 μM) in Caco-2 cells (intestinal epithelial cells) without inhibition of other efflux transporters (MRP2, MRP4, and BCRP) or the bile salt export protein at clinically relevant concentrations (PK1006, PK0904). These data suggest a clinical interaction between RFX and other compounds that undergo efflux via P-gp and other transport proteins is unlikely.

RFX does not inhibit hERG channels *in vitro*, indicating minimal risk of clinical QT interval prolongation (PD0901, RFHE3002PK and RFPK1010).

In vivo pharmacokinetic interactions

In Vivo studies

With respect to hepatically impaired subjects, while the C_{max} of RFX is higher than in healthy subjects, the plasma concentration is still 300 to 400 fold lower than rifampin concentrations (10-50 μM) that resulted in approximately 4 fold CYP3A4 induction *in vitro*. Hence, oral administration of RFX unlikely to cause clinically relevant induction of hepatic CYP3A4 *in vivo* even in hepatically impaired subjects.

Co-administration of rifampin and the oral contraceptive pill (OCP) has resulted in a failure of the OCP and unplanned pregnancy in cases where OCP has been the only means of contraception used. Hence several studies have explored whether the OCP can be co-administered with RFX. RFX 200 mg td x 3 days in healthy female volunteers *in vivo* did not significantly affect the PK of single doses of oral midazolam (MDZ), IV MDZ or oral Ortho-Cyclen® (RFDI1002, RFDI1001). Study RFDI1009 assessed the potential for a drug interaction between RFX, 1650 mg/day, administered as one 550 mg tablet td and concomitantly administered ethinyl estradiol (EE) and norgestimate (Ortho Tri-Cyclen Lo; an OCP) in healthy subjects. RFX 550 mg td for 7 days resulted in systemic exposure parameters (AUC_{0-t} and AUC_{0-∞}) that were quantitatively similar following OC plus RFX

when compared with OC alone for the analytes EE, 17-deacetylnorgestimate (NGMN) and norgestrel (NG). Mean C_{max} values were slightly lower after with co-administration for the 3 analytes. Altered efficacy of OCPs containing EE and norgestimate is not expected during concomitant administration with RFX.

P-glycoprotein

Results of digoxin transport competitive inhibition experiments (*PK0903*) indicated that RFX was not an effective inhibitor of P-gp activity and is unlikely to cause drug-drug interactions with other substrates of P-gp.

Evaluator's overall comments on pharmacokinetic interactions

No data to suggest any PK interactions of significance when RFX is co-administered with drugs metabolised through the cytochrome P450 or that are substrates of P-gp.

Exposure relevant for safety evaluation

Phase I studies in conjunction with the Phase II/III data support the clinical target dose and schedule of RFX550mg bd. The safety data arising from the Phase I program is summarised in the section on *Clinical Safety* below.

Evaluator's overall conclusions on pharmacokinetics

The Phase I PK program was reasonably comprehensive and detailed.

Pharmacodynamics

Introduction

RFX is a member of rifamycin family, which includes both the natural rifamycins, that is, O, B, S, SV and synthetic rifamycins (rifampicin, rifabutin and RFX). The rifamycin antibiotics are fermentation products of *Amycolatopsis mediterranea*. This class of antibiotics inhibits the DNA-dependent RNA-polymerase of the target microorganisms, leading to the suppression of initiation of chain formation during RNA synthesis. RFX may also alter virulence factors of the gut bacterial pathogens without killing. RFX is very poorly systemically absorbed (<0.4%) and this leads to extremely low plasma concentrations and very high stool concentrations. Since the drug is not systemically available and the therapeutic site of action is the GI tract, plasma levels cannot be used to determine bacterial susceptibility to RFX^{16,17} and MIC and PK/PD data must be interpreted differently from agents that are systemically absorbed.

As RFX is poorly absorbed after oral administration, the drug is selectively active in the GI tract and could be viewed as a topical agent in the gut lumen. As a consequence, RFX has been investigated in a variety of GI diseases where disturbance of the host's intestinal flora is implicated in pathogenesis such as travellers' diarrhoea (TD), HE, Crohn's disease, pouchitis with ulcerative colitis (UC) and small intestinal bacterial overgrowth.

RFX MIC₅₀ and MIC₉₀ ranges have been established for 1,607 clinical isolate pathogens associated with infectious diarrhoea. Details of these data are provided below.

¹⁶Brown EL, Xue Q, Jiang ZD, Xu Y, Dupont HL. Pretreatment of epithelial cells with RFX alters bacterial attachment and internalization profiles. *Antimicrob Agents Chemother*. 2010;54:388-96.

¹⁷Debbia EA, Maioli E, Roveta S, Marchese A. Effect of RFX on bacterial virulence mechanism at supra- and sub-inhibitory concentrations. *J Chemother* 2008; 20;186-4.

Two mechanisms of RFX resistance exist, the first is similar to the parent drug, that is, chromosomal one-step alteration in the drug target, DNA-dependent RNA. This differs from plasmid-mediated resistance that is easily acquired by susceptible bacteria after treatment with other antibiotic classes such as aminoglycosides, sulphonamides and macrolides. To date, no plasmid or transposon resistance documented for this class suggesting the risk of horizontal dissemination of RFX resistance to other bacteria is unlikely. The second mechanism of resistance appears to be through metabolic modification via specific amino acid substitutions of the cell membranes of resistant mutant bacteria. RFX, like the parent drug, has activity against *Mycobacterium tuberculosis* but because of poor oral absorption it has a very limited action on the illness *in vivo* and more importantly a low risk of rifampicin cross-resistance.

Spontaneous RFX-resistance has been reported in a number of gut organisms; enterococci, *Clostridium difficile*, *Clostridium perfringens* and *Bacteroides fragilis*. With respect to *C.difficile*, there is no cross resistance with RFX-resistance strains and metronidazole or vancomycin, the mainstay of *C.Difficile* diarrhoea treatment¹⁸.

Finally, RFX appears effective in lowering the viability and virulence of bacteria even when they have developed “resistance” to the compound, suggesting that in some way their physiological functions are compromised^{17, 19}.

RFX was approved in the European Union (EU) in 1987 for acute and chronic intestinal infections by Gram-positive and Gram-negative bacteria, for the treatment of travellers’ diarrhoea, as co-adjuvant in the treatment of hyper-ammonaemia, and for pre and post operative prophylaxis of GI tract surgery; it has been approved in USA since 2004 for the treatment of TD and since 2010 for reduction in risk of overt HE recurrence. In summary, RFX is a minimally absorbed antibiotic, as its microbiological activity in the gut is the likely mechanism of its efficacy in HE.

Mechanism of action

The neurological symptoms of HE are attributed to global central nervous system (CNS) depression from nitrogenous compounds and other gut-derived neurotoxins. These nitrogenous compounds and gut-derived neurotoxins are by-products of endogenous bacterial metabolism in the gut and gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. RFX inhibits RNA synthesis and as such has a broad spectrum of activity against Gram-positive and Gram-negative, aerobic, and anaerobic enterobacteria¹⁸. The down-stream effect of this antibiotic activity is the reduction in the production in nitrogenous compounds, predominantly ammonia by gut micro-organisms and a reduction in HE episodes. However, the ammonia hypothesis has been debated for a number of reasons; firstly, observations that approximately 10% of patients with significant HE have normal serum ammonia levels; secondly, cirrhotic patients can have elevated ammonia levels without HE; thirdly, ammonia does not induce the classic electroencephalographic (EEG) changes associated with HE.

Spectrum of microbiological activity

The *in vitro* antimicrobial spectrum of RFX activity was assessed in several studies evaluating 1607 isolates from subjects with infectious diarrhoea. For all isolates in all studies, RFX MICs were substantially lower than expected faecal concentrations of RFX,

¹⁸Jiang ZD, DuPont HL. RFX: in vitro and in vivo antibacterial activity--a review. *Chemotherapy*. 2005;51 Suppl 1:67-72.

¹⁹Huang DB, DuPont HL. RFX-a novel antimicrobial for enteric infections. *J Infect*. 2005;50:97-106.

determined to be approximately 8000 µg/mL or approximately 8 fold higher than the highest MIC (MIC50 and MIC90 ranges for the 1607 isolates were 0.001-128 µg/mL and 0.005-256 µg/mL, respectively) established for these clinical pathogens.^{20, 21, 22, 23} *Clostridium* species were found to be some of the most sensitive organisms to RFX, with MIC90 ranging from 0.005-2 µg/mL.^{24, 25, 26} The MIC90 for *E. coli* ranged from 60 µg-128 µg/mL with 1 study reporting a MIC90 of >200 µg/mL.^(27; N2129). In separate studies, MIC ranges were established for other organisms such as *Bacteroides*, *Bifidobacterium*, *Enterobacter cloacae*, *Fusobacterium*, *K. pneumoniae*, *Peptostreptococcus*, *Prevotella*, *Proteus species (spp)*., *Pseudomonas aeruginosa*, *Serratia spp.* and *Streptococcus*. In another study evaluating the antibacterial activity of RFX on bacteria cultured from stool samples collected from subjects with HE (²⁸; RFHE8501), antibacterial effect of RFX was strongest against aerobic and anaerobic cocci, producing a bactericidal effect greater than 99% against these bacteria. RFX was also active against anaerobic rods, reducing the quantity of *Clostridium sporogenes* (sp) from 1.0×10^8 through 4.5×10^6 , *Bacteroides sp* from 4.8×10^9 to 1.1×10^8 and *Fusobacterium sp* from 1.1×10^7 through 2.0×10^6 . RFX has low anti-bacterial activity against enterobacteriaceae. When the antimicrobial activity against enteroaggregative *E. coli* (EAEC) and enterotoxigenic *E. coli* (ETEC) was compared between RFX and 6 standard antimicrobial agents, RFX had better or comparable activity to most of the agents evaluated, including ampicillin, chloramphenicol, tetracycline and trimethoprim.

Primary pharmacology

As described in the section of *Pharmacokinetics* this antibiotic has very poor systemic absorption and is largely excreted intact in the faeces.

Secondary pharmacology

Not applicable due to poor systemic absorption.

²⁰Hooper LV, Gordon JI. (2001). Commensal host-bacterial relationships in the gut. *Science* 292: 1115-1118

²¹Ripa S, Mignini F, Prenna M, Falcioni E. In vitro antibacterial activity of rifaximin against *Clostridium difficile*, *Campylobacter jejunii* and *Yersinia spp.* *Drugs Exp Clin Res.* 1987; 13:483-8;

²²Venturini AP, Marchi E. In vitro and in vivo evaluation of L/105, a new topical intestinal rifamycin. *Chemioterapia.* 1986; 5: 257-62.

²³Jiang Z-D, Ke S, Palazzini E, et al. (2000). *In Vitro* Activity and Fecal Concentration of Rifaximin after Oral Administration. *Antimicrob. Agents Chemother* 44(8):2205-2206

²⁴Marchese A, Salerno A, Pesce A, Debbia EA, Schito GC. In vitro activity of rifaximin, metronidazole and vancomycin against *Clostridium difficile* and the rate of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia producing species. *Chemotherapy* 2000; 46: 253-66.

²⁵Hecht DW, Galang MA, Sambol SP, Osmolski JR, Johnson S, Gerding DN. In vitro activities of 15 antimicrobial agents against 110 toxigenic *Clostridium difficile* clinical isolates collected from 1983 to 2004. *Antimicrob. Agents Chemother.* 2007; 51: 2716-19.

²⁶Jiang Z-D, DuPont HL, La Rocco M, Garey KW. In vitro susceptibility of *Clostridium difficile* to rifaximin and rifampin in 359 consecutive isolates at a university hospital in Houston, Texas. *J Clin Pathol.* 2010; 63: 355-8;

²⁷Gomi H, Jiang Z-D, Adachi JA, Ashley D, Lowe B, Verenkar MP et al. In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions. *Antimicrob Agents Chemother* 2001; 45: 212-6.

²⁸Testa R, Eftimiadi C, Sukkar GS, De Leo C, Rovida S, Schito GC, et al. A non-absorbable rifamycin for treatment of hepatic encephalopathy. *Drugs Exptl Clin Res.* 1985; 11: 387-92.

Relationship between plasma concentration and effect

This is not applicable for this agent; oral absorption is very poor, mode of action rests with the poor oral bioavailability and high intra-luminal gut concentrations.

Relationship between faecal concentrations, MIC of enteropathogens, resistance, impact on normal faecal flora

Generally, MIC breakpoints are established on systemic exposure levels. However, plasma levels cannot be used to determine bacterial susceptibility to RFX since the drug is not systemically available and the therapeutic site of action is the GI tract. Faecal concentration of RFX may be the most clinically relevant measure for determining bacterial susceptibility. The mean faecal concentration of RFX following 3 days of treatment with RFX 800 mg daily was approximately 8000 µg per gram of faeces (²³; PD0001). Assuming equivalent densities of faecal mass and water (1 g/mL), faecal concentrations on a µg/g basis are equivalent to concentrations on a µg/mL basis. RFX is believed to be only partially dissolved when travelling through the GI tract. The actual availability of solubilised RFX along the gut wall, where the microbes and host interact, is unknown. RFX is only effective for treating infections and GI microbial imbalances that are localised to the gut and not suitable for treating systemic infections caused by invasive organisms, that is, *Campylobacter jejuni* or *Salmonella spp* (RFID3001).

The antibacterial properties of RFX include bactericidal activity at RFX concentrations greater than or equal to the MIC and alterations in bacterial virulence²⁹ and physiological functioning of epithelial cells³⁰ which have been observed at sub-MIC concentrations.

Ranges for the RFX MIC that inhibits 50% of microorganism growth (MIC50) and MIC that inhibits 90% of microorganism growth (MIC90) have been established for 1607 clinical isolate pathogens associated with infectious diarrhoea as described above.

RFX shortens the duration of TD and non-dysenteric diarrhoeal illness due to EAEC, ETEC and *Shigella sonnei* without major alteration of aerobic faecal flora and without important side effects.^{31, 32, 33,34} In at least 2 clinical studies, there appears to be a rapid return to sensitive bacterial strains, especially in aerobic species, after RFX treatment ends.^{35,36, 37} The lower rate of faecal eradication of pathogens compared with other commonly used antibacterial drugs and lack of alteration of gut flora suggest that RFX has a different mechanism of action than other commonly used drugs in enteric bacterial infection, such

²⁹Jiang ZD, Ke S, DuPont HL. Rifaximin-induced alteration of virulence of diarrhoea-producing *Escherichia coli* and *Shigella sonnei*. *Int J Antimicrob Agents*. 2010; 35: 278-81.

³⁰Brown EL, Xue Q, Jiang ZD, Xu Y, Dupont HL. Pretreatment of epithelial cells with RFX alters bacterial attachment and internalization profiles. *Antimicrob Agents Chemother*. 2010;54:388-96

³¹DuPont HL, Ericsson CD, Mathewson JJ, Palazzinic E, DuPont MW, Jiang ZD, et al. Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. *Digestion* 1998; 59: 708-14.

³²DuPont HL, Jiang ZD, Ericsson CD, Adachi JA, Mathewson JJ, DuPont MW, et al. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001; 33: 1807-15.

³³DuPont HL, Jiang ZD. Influence of rifaximin treatment on susceptibility of intestinal Gram negative flora and enterococci. *Clin Microbiol Infect Dis* 2004; 10: 1009-11.

³⁴DuPont HL, Jiang ZD, Okhuysen PC, Ericsson CD, de la Cabada FJ, Ke S, et al. A randomized, double-blind, placebo-controlled trial of RFX to prevent travelers' diarrhea. *Ann Intern Med*. 2005;142:805-12. Erratum in: *Ann Intern Med*. 2005;143:239.

³⁵Brigidi P, Swennen E, Rizzello F, Bozzolasco M, Matteuzzi D. Effect of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. *J Chemother* 2002; 14: 290-5.

³⁶De Leo C, Eftimiadi C, Schito GC. Rapid disappearance from the intestinal tract of bacteria resistant to rifaximin. *Drugs Exptl Clin Res*. 1986; 12: 979- 81.

³⁷Eftimiadi C, Deleo C, Schito GC. Treatment of hepatic encephalopathy with L/105, a new non-absorbable rifamycin. *Drugs Exp Clin Res* 1984; 10: 691-6.

as the fluoroquinolones and aminoglycosides.^{32, 38, 26} For example, median coliform log counts in stool from healthy subjects receiving RFX 200 mg to 600 mg/day for 7 or 14 days were not different from subjects receiving placebo³⁴; in contrast, treatment with the fluoroquinolone norfloxacin 400 mg once daily for 7 or 14 days resulted in significant reductions in aerobic faecal flora and eradication of aerobic Gram-negative bacilli in healthy subjects³⁸.

RFX does not promote the emergence of bacterial cross-resistance to rifampin, as has been demonstrated in studies examining *C. difficile* *in vivo* and *C. difficile*, *E. coli* and *M. tuberculosis* *in vitro* (PD9303; ³³; PD1001; ²⁶).

Pharmacodynamic interactions with other medicinal products or substances

None; some evidence of adjunctive activity when dosed *with* ciprofloxacin in subjects with chronic treatment-resistance, that is, no response to antibiotics given for at least 4 weeks) ulcerative colitis (UC) related pouchitis (*RFUC9702*).

Genetic differences in pharmacodynamic response

None expected due to poor systemic absorption.

Evaluator's overall conclusions on pharmacodynamics

The PD studies establish that RFX has a broad spectrum of activity against many non-invasive GI pathogens and normal faecal flora. Variable schedules of oral dosing achieve very high levels of intra-luminal RFX well above the MIC50 and MIC90 for most of these organisms. There appears to be little to no selection of resistance although most data is derived from relatively short-term exposure to RFX, that is, in the setting of treatment or prevention of TD. The selection of the 550 mg bd dose for prevention of HE recurrence is presumably on the basis of ease of dosing and to reduce pill burden as there is no head-to-head study comparing the 550 mg bd dose to the other dosing schedules utilising the 200 mg tablet strength. Moreover, over short exposure (7 days) there was no demonstrable difference in PSE index when doses of between 600 mg-2400 mg RFX/day were utilised. Further justification for the dosing proposed for this indication is presented in the section on *Efficacy* below.

Efficacy

Introduction

Recurrent, overt, episodic HE is common among patients with liver cirrhosis. HE may occur at any age but the peaks parallel those of fulminant liver disease (peak = 40s), and cirrhosis (peak = late 50s). Males and females are affected in roughly equal proportions, reflecting the underlying liver disease. HE may be associated with acute liver failure, portal-systemic bypass with no intrinsic hepato-cellular disease or cirrhosis and portal hypertension with portal-systemic shunting of blood; HE associated with the latter is most common. HE manifests as a continuum of mental status deterioration, psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and in severe forms, coma and death. Changes may be

³⁸Johnson PC, Ericsson CD, Morgan DR, Dupont HL, Cabada FJ. Lack of emergence of resistant fecal flora during successful prophylaxis of travelers' diarrhea with norfloxacin. *Antimicrob Agents Chemother* 1986;30:671-74;

observed in personality, consciousness, behaviour and neuromuscular function. Neuromotor signs may include hyperreflexia, rigidity, myoclonus and asterixis (a coarse, myoclonic “flapping” muscle tremor) (Conn). HE is associated with high rates of morbidity and mortality and the occurrence of an HE episode of Conn score 2 in patients with cirrhosis was associated with a 4 fold increase in the risk of death.³⁹

The proposed indication for RFX 550 mg bd is for the prevention of the recurrence of HE in adults. The requested MA is based on the clinically significant and statistically significant results in favour of RFX versus placebo controlled Study RFHE3001, safety data from Studies RFHE3001 and RFHE3002, supportive data in published clinical trials of RFX used in other setting, particularly TD and completion of the clinical PK program.

The mainstay of treatment of HE in the Australian setting, is the use of cathartics, that is, non-absorbable disaccharides to reduce systemic ammonia levels by reducing colonic bacterial load via increasing throughput, acidification of the gut lumen to favour the transit of ammonia and inhibition of ammoniogenic coliform bacteria, leading to increased levels of nonammoniogenic lactobacilli. i.e. Lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol), the latter is not available in the USA and this is one of the reasons that lactulose has been utilised in the RFX development program (largely US based) and not lactitol.

The ideal dose of these agents is one which leads to 2-4 loose stools per day and this titration of dose can be difficult to manage for many patients particularly if there is some degree of HE-related confusion to begin with. Moreover, overdosage can result in ileus, severe diarrhoea, electrolyte disturbances and hypovolemia, the latter paradoxically can worsen HE. In cases of severe and life-threatening HE, high doses of lactulose, for example 30 mL 2-4 hrs can be administered. Other options include the use of neomycin and other antibiotics such as metronidazole, oral vancomycin, paromomycin and oral quinolones, are administered in an effort to decrease the colonic concentration of ammoniogenic bacteria. But all of these are associated with adverse drug effects include ototoxicity and nephrotoxicity with neomycin because of its systemic absorption (albeit low) if administered chronically, in particular in the setting of liver cirrhosis.

One of the main ways to assess changes in HE status is using the PSE index⁴⁰ which is a component score that included scores for mental state (Conn score), asterixis, venous ammonia levels, number connection test (NCT) and EEG changes.

Dose response studies and main clinical studies

Dose response studies

Three main factors were considered in the dosing schedule of 550 mg bd for the pivotal Phase III studies for the proposed indication:

1. The transit time of the drug as demonstrated in scintigraphy study (RFPK1002) revealed a rapid GI transit time of RFX 200 mg tablets. Therefore, bd dosing was chosen in order to maintain high RFX concentration in the gut;
2. Dose-dependent reductions in small intestinal bacterial overgrowth of 17%, 26%, 60% and 80% were reported at daily doses of 600, 800, 1200 and 1600mg per day,

³⁹Stewart CA, Malichoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transpl.* 2007; 13: 1366-71

⁴⁰ The severity of symptoms of hepatic encephalopathy can be described using the portal-systemic encephalopathy (PSE) score and index. Each component is assigned 0 to 4 points based on the severity of the symptom.

respectively, suggesting that the 1200 mg dose level would be effective in the reduction of gut flora in patients with HE^{41, 42} and this reduction would translate into reductions in systemic ammonia levels thought to drive HE;

3. The efficacy of RFX 1200 mg/day (given as 2x200 mg td) in the following settings:
 - a. Based on past clinical experience with RFX in patients with HE treated *chronically* (including published studies; see below) and other subject populations (IBS). RFX was safe and effective in subjects with HE at doses of 1200 mg per +/- concomitant lactulose.⁴³ In a 6 month study of RFX versus neomycin (14 days on-treatment and 14 days off-treatment per month)⁴⁴, RFX 1200 mg/day versus neomycin (3 g/day) had comparable efficacy to neomycin in patients with HE;
 - i. A small pilot study⁴⁵ showed that RFX 1200 mg/day for 3 months (n = 14) or RFX 1200 mg/day plus lactitol (n = 13) was more effective than lactitol alone (n = 13). The proportions of subjects who achieved normalisation of blood ammonia levels by end of treatment were significantly higher in the groups treated with RFX (p <0.05 in favour of the RFX versus lactitol alone). In addition, 66.7% of RFX subjects, 54.6% in RFX/lactitol group and 20.0% in lactitol group achieved complete normalisation in mental status (Conn score = 0) by the end of treatment (p <0.05 in favour of the RFX groups versus lactitol alone);
 - ii. In another small pilot study⁴³ of RFX 1200 mg/day plus lactulose (n = 20) versus lactulose alone (n = 20) over 3 months, there were greater improvements and/or more rapid improvements in the RFX group. RFX was significantly more effective than lactulose alone in decreasing the severity of PSE (p <0.05 after 2 weeks), decreasing EEG irregularities (p <0.01 after 15 days and p <0.05 after 30 days) and improving the subjects' mental states (p <0.05 after 60 days and p <0.02 after 90 days of therapy).
 - iii. In the 6 month study of RFX 1200 mg/day versus neomycin (3 g/day)⁴⁴, subjects in both treatment groups experienced significant decreases from baseline in HE grade and blood ammonia levels. Among 49 evaluable subjects (25 RFX, 24 neomycin), statistically significant reductions in HE grade from baseline beginning on Day 30 (p <0.001) were experienced in both treatment groups. Significant decreases in blood ammonia levels (p <0.001) occurred after both RFX and neomycin.
 - b. In 3 acute treatment controlled clinical studies, *RFHE9702*, *RFHE9701*, and *RFHE9901*, subjects with ongoing symptoms of HE received RFX or comparator (lactitol or placebo) for up to 15 days:
 - i. In the *acute* treatment, dose-ranging study of subjects with ongoing HE, *RFHE9702*, there was a dose-dependent *trend* (p = 0.28 by using analysis of covariance) in improvements in the PSE index and no further improvement

⁴¹Lauritano EC, Gabrielli M, Lupascu A, Santoliquido A, Nucera G, Scarpellini E, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2005; 22: 31-5.

⁴²Scarpellini E, Gabrielli M, Lauritano EC, Lupascu A, Merra G, Cammarota G, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2007; 25: 781-6.

⁴³Fera G, Agostinacchio F, Nigro M, Schiraldi O, Ferrieri A. Rifaximin for the treatment of hepatic encephalopathy. *Eur J Clinical Res* 1993; 4: 57-66.

⁴⁴Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifamycin, for treatment of hepatic encephalopathy. A double-blind, randomized trial. *Curr Med Res Opin.* 1997; 13: 593-601.

⁴⁵Lauritano EC, Gabrielli M, Lupascu A, Santoliquido A, Nucera G, Scarpellini E, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2005; 22: 31-5.

was observed at the 2400 mg dose. In a supplementary analysis, the Jonckheere-Terpstra test, was performed to evaluate the null hypothesis that the distribution of PSE index results was the same across dose groups showed a $p=0.0586$, indicating a trend in improvements in PSE index across the dose groups used, that is, 600 mg/1200 mg/2400 mg RFX per day over 7 days;

- ii. *RFHE9701*. RFX 1200mg/day was compared to a standard dose of lactitol. There were statistically significant between-group differences in the changes in PSE index and venous ammonia levels in favour of RFX; higher proportion of RFX subjects were considered cured, that is, venous ammonia normalised and mental state/Conn score of 0 at end of treatment;
- iii. *RFHE9901*. In this study, RFX 1200mg/day did not show any benefit in regards to the primary endpoint, improvement in Conn score versus placebo, although there were significant improvements in asterixis grade. The reasons for this are unclear.

In summary, the 1100 mg/day dose (550 mg tablets bd) was chosen for *RFHE3001* and *RFHE3002* based on results showing the effectiveness of RFX 1200 mg/day (2x200 mg tablets td) in patients with HE in the chronic setting *and* in the dose finding, acute treatment studies as described above and in other acute treatment studies.

Main (pivotal) studies

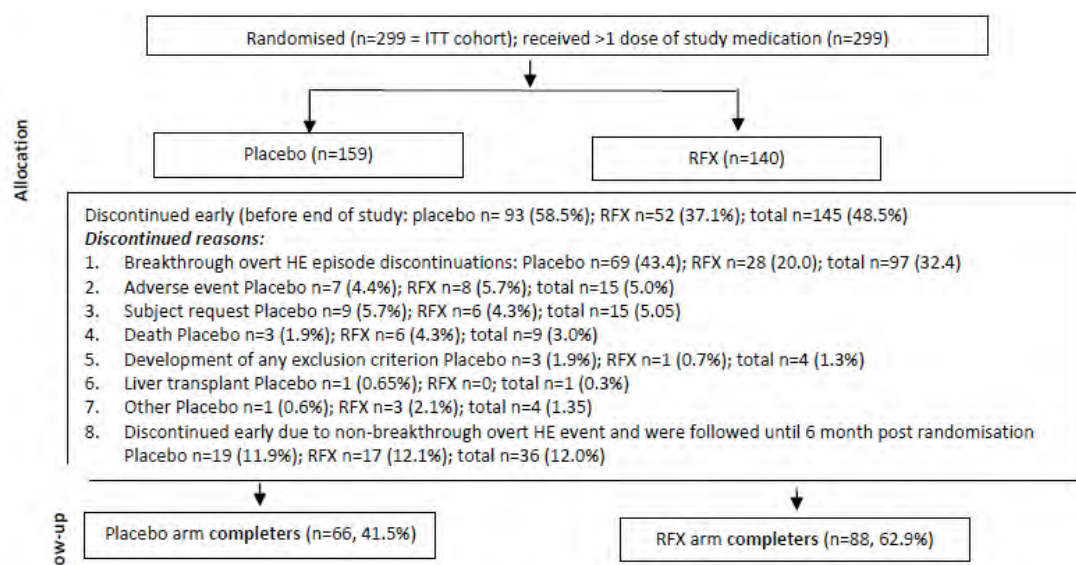
The data provided below refers to *RFHE3001* and the open label extension phase of this study, *RFHE3002*.

RFHE3001

Pivotal Phase III, randomised, multi centre, double blind study to evaluate the efficacy, safety and tolerability of RFX 550 mg bd for 6 Months in Preventing HE. The study was conducted as per Good Clinical Practice (GCP).

Methods: Detailed in the sponsor's study report (see Figure 2 below).

Figure 2. Results. Participant flow.



Numbers analysed in the ITT totalled 299 subjects, that is, all randomised subjects received at least 1 dose of study medication. In assessing treatment compliance

(determined by counts of returned versus dispensed tablets) this was high in both treatment groups. Mean compliance percentages were 101.1% (RFX) versus 98.1% (placebo). Compliance of $\geq 80\%$ was observed for 84.3% (RFX) and 84.9% (placebo) over the course of the study.

Completed

Placebo: 41.5% completed; 58.5% discontinued early, the main reason was breakthrough overt HE episode related discontinuation in 69 subjects (43.4%);

RFX: 62.9% completed; 37.1% discontinued early, the main reason was breakthrough overt HE episode related discontinuation in 28 subjects (20%)

Summary baseline demographics of all randomised subjects:

Median age was 56.0 years (range, 21-82 years) and 19.4% of subjects were ≥ 65 years of age; White (86%), male (60.9%). A total of 205, 14 and 80 subjects were randomised in the study from the United States, Canada and Russia, respectively. The relative distribution of subjects by demographic characteristic was comparable between treatment groups in the intent-to-treat (ITT) population. The percentage of women subjects was higher in Russia (52.5%) than North America (34.2%). Other demographic characteristics were similar among the overall ITT population, subjects in North America and subjects in Russia.

All subjects in the study had a history of overt, episodic HE associated with advanced liver disease that was diagnosed by evidence of ≥ 2 episodes of overt HE (Conn score of ≥ 2) within 6 months prior to screening. At the baseline assessment, subjects were in remission with a Conn score of 0 or 1. Baseline Conn scores were 0 for 66.9% of subjects and 1 for 33.1% of subjects. Most subjects had asterixis grade 0 (68.2%) or grade 1 (28.8%). The mean (\pm standard deviation (SD)) duration of current verified remission from HE (time since the most recent verified HE event) was 71.1 (± 49.62) days; most subjects experienced 2 (69.6%) or 3 (21.4%) episodes of HE during the 6 month interval prior to study entry.

The mean time since first diagnosis of advanced liver disease was 56.2 months (range, 1.7 to 323.4 months). Mean (\pm SD) Model for End-Stage Liver Disease (MELD)⁴⁶ score was 12.9 (± 3.80); most subjects had MELD scores of either ≤ 10 (27.4%) or 11 to 18 (63.5%) at baseline.

A total of 273/299 subjects (91.3%) received lactulose as a prior medication *and* as a concomitant medication during the study. The percentages of subjects who took lactulose were similar between the placebo (91.2%) and RFX (91.4%) groups during the course of the study. Moreover, daily lactulose use over the total 6 month treatment period and lactulose use by study day were similar between arms. Mean (\pm SD) daily lactulose use was 3.14 (± 2.096) cups/day in the RFX group and 3.51 (± 2.592) cups/day in the placebo group. (NB: One cup of lactulose is equal to 15 mL (10 g lactulose/15 mL).

In summary: Primary Analysis in the ITT group (derived as shown in the diagram above):

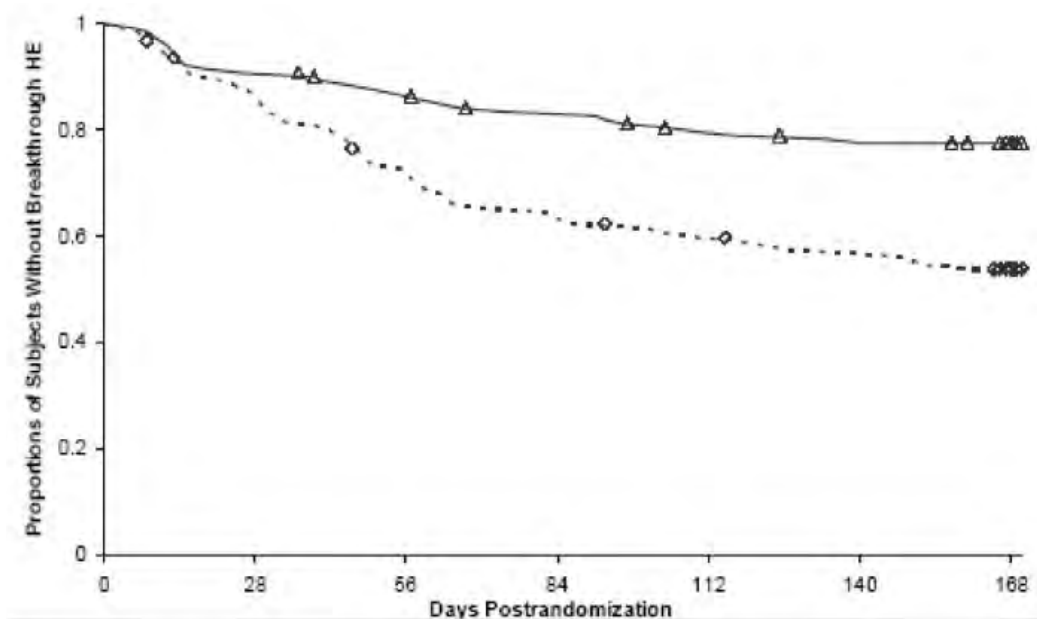
1. Breakthrough overt HE episodes occurred in 31/140 (22%) subjects in the RFX group and by 73/159 (45.9%) subjects in the placebo group during the 6 month period since randomisation (up to Day 170). Comparison of Kaplan-Meier estimates of time to breakthrough overt HE between groups showed a highly significant protective effect

⁴⁶ MELD is a scoring system for assessing the severity of [chronic liver disease](#). MELD uses the patient's values for serum [bilirubin](#), serum [creatinine](#) and the [international normalized ratio for prothrombin time \(INR\)](#) to predict survival.

of RFX ($p < 0.0001$). The HR for the risk of experiencing breakthrough overt HE in the RFX group relative to the risk in the placebo group was 0.421 (95% confidence interval [CI]: 0.276 to 0.641) during the 6 month treatment period, that is, RFX reduces the risk of experiencing breakthrough overt HE of approximately 58% (Figure 3);

- Because subjects who did not experience breakthrough overt HE were followed after study discontinuation, the primary efficacy endpoint was analysed up to last contact in Results were similar to the analysis of the 6 month treatment period, that is, a total of 34/140 subjects in the RFX group and 73/159 subjects in the placebo group had breakthrough overt HE during the Treatment Period *plus follow-up*; HR 0.461 (CI: 0.307 to 0.693) ($p = 0.0001$).

Figure 3. Time to first breakthrough overt HE episode (up to Day 170). ITT population. ○=placebo and △=RFX



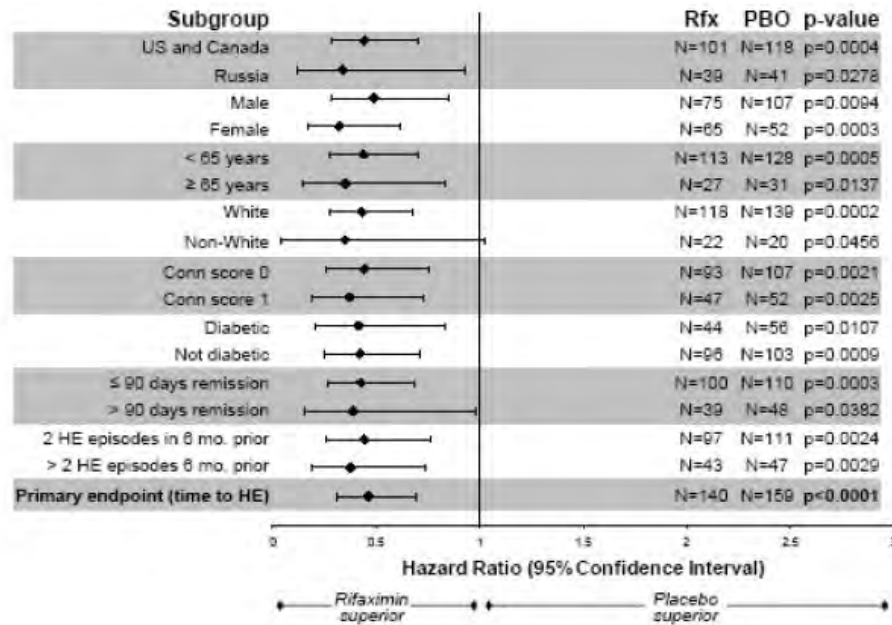
- Predictors of time to first breakthrough over HE Episode:** To investigate the potential effect of prognostic factors on breakthrough overt HE episode, a log rank test stratified on each covariate was performed. The following prognostic factors were examined: Sex (male versus female); Age; Race (White versus non-White); Geographic analysis Region (North American versus Russia); MELD Level; Conn Score (0 versus 1); Diabetes at Baseline (Yes versus No); Duration of current verified remission; Number of HE Episodes within the past 6 months prior to randomisation.

Strong independent predictors of breakthrough overt HE episodes were the baseline age ($p=0.0160$), MELD score ($p=0.0003$), duration of current verified remission ($p=0.1089$), and number of prior HE episodes ($p=0.0022$). Note that prior lactulose use was not analysed as a covariate because $\geq 90\%$ of subjects in each treatment group were receiving lactulose prior to study entry.

To control for these factors on outcome due to chance imbalances between treatment groups, multivariate analysis was performed using the Cox proportional hazards model including treatment group, age, MELD score, duration of current verified remission and number of prior HE episodes. A hazard ratio (RFX to placebo) of 0.403 (95% CI: 0.264 to 0.617) ($p < 0.0001$) was noted. These data show that RFX treatment still results in a 60% reduction versus placebo in the risk of experiencing a

breakthrough overt HE episode. The most influential prognostic factors in the multivariate analysis were age ($p = 0.0225$) and baseline MELD score ($p = 0.0005$).

Figure 4. Time to first breakthrough overt HE episode by subgroup (up to 6 months of treatment Day 170. ITT population. This figure shows HRs for the risk of experiencing breakthrough overt HE (RFX group divided by placebo group) for each subgroup, 95% CI intervals and p values for differences between the RFX and placebo groups as determined by the Cox proportional hazards model.



4. Secondary endpoints analysed in a hierarchical manner.

- Hospitalisations due to HE were reported for 19/140 subjects and 36/159 subjects in the RFX and placebo groups, respectively. RFX had a significant protective effect against HE related hospitalisation during the 6 month treatment period; hazard ratio in the RFX group relative to placebo was 0.500 (95% CI: 0.287 to 0.873) ($p = 0.0129$) for the risk of HE related hospitalisation. Subjects in the RFX group had a 50% reduction, when compared with placebo, in the risk of hospitalisation due to HE during the 6 month treatment period.
- Increases in Conn score were reported for 37/140 (26.4%) subjects and 77/159 (48.4%) subjects in the RFX and placebo groups, respectively. A highly significant protective effect of RFX was observed; hazard ratio in the RFX group relative to placebo was 0.463 (95% CI: 0.312 to 0.685) ($p < 0.0001$) for the risk of experiencing an increase in Conn score (worsening in mental status) during the 6 month treatment period;
- Increases in asterixis grade were reported for 32/140 (22.8%) subjects and 50/159 (31.4%) subjects in the RFX and placebo groups, respectively. A protective effect of RFX against an increase in asterixis grade was observed that showed a trend toward statistical significance; hazard ratio in the RFX group relative to placebo was 0.646 (95% CI: 0.414 to 1.008) ($p = 0.0523$) for the risk of experiencing an increase in asterixis grade during the 6 month treatment period.

Other secondary analyses of importance

1. Minimal differences between placebo and RFX groups were observed in the changes from baseline in CLDQ fatigue scores. Mean (SD) fatigue scores were 3.28 (± 1.326) versus 3.34 (± 1.406) at baseline and 3.57 (± 1.527) versus 3.51 (± 1.529) in the RFX and placebo groups, respectively;
2. In the current study, venous ammonia levels were highly variable over the course of the study. However, subjects in the RFX group had greater reductions in venous ammonia levels when compared to placebo treated subjects and this between-group difference showed a statistical trend in favour of the RFX group ($p=0.0818$).

Safety data from this study is included in the section on *Safety* and Table 7.

Conclusion

RFX 550mg bd results in a 57.9% reduction when compared with placebo in the risk of experiencing breakthrough overt HE during the course of this study. It is noteworthy that more than 90% of subjects were receiving lactulose at baseline and remained on this agent during the study.

Ancillary analyses

RFPE3002Pk was a PK substudy. PK sampling was performed after at least 7 consecutive days of oral dosing with RFX 550 mg bd tablet. PK sampling over 12 hrs post dose.

Safety data from this study is included in the section on *Safety* and Table 7.

Table 7a. Summary of clinical safety for the pivotal Phase III study RFHE3001

	RFHE3001	
	placebo	RFX
Mean exposure in days (SD)	105.7 (62.71)	130.3 (56.47)
Treated, n	159	140
Completed the treatment phase of 6 months	66 (41.5%)	88 (62.9%)
Discontinued treatment phase, n(%)	93 (58.5%)	n=52 (37.1%)
Breakthrough overt HE episode discontinuations (primary endpoint which required discontinuation as per the protocol)	n=69 (43.4)	RFX n=28 (20.0)
AE	n=7 (4.4%)	n=8 (5.7%)
Subject request	n=9 (5.7%)	n=6 (4.3%)
Death	n=3 (1.9%)	n=6 (4.3%)
Development of any exclusion criterion	n=3 (1.9%)	n=1 (0.7%)
Liver transplant	n=1 (0.65%)	n=0 (0%)
other	n=1 (0.6%)	n=3 (2.1%)
Discontinued early due to non-breakthrough overt HE event and were followed until 6 month post randomisation	n=19 (11.9%)	17 (12.1%)

Table 7b. AE, deaths, study discontinuation and dose modifications in RFHE3001 and in the long term RFX experience population.

	RFHE3001		Long-term RFX experience population
	Placebo (n=159) PEY 46.0 n (%)	RFX (n=140) PEY=50 n (%)	All RFX patients (n=336) PEY =251.9 n (%)
Subjects with any Treatment-emergent AE	127 (79.9)	112 (80)	293 (87.2)
TEAE by intensity			
Serious	49 (30.8)	37 (26.4)	139 (41.4)
moderate	54 (34.0)	52 (37.1)	103 (30.7)
mild	24 (15.1)	23 (16.4)	51 (15.2)
TEAE related to study drug	34 (21.4)	27 (19.3)	46 (13.7)
Serious TEAEs	63 (39.6)	51 (36.4)	165 (49.1)
TEAEs resulting			
discontinuation	45 (28.3)	30 (21.4)	72 (21.4)
All deaths	11 (6.9)	10 (7.1)	36 (10.7)
Deaths while on study drug	6 (3.8)	6 (4.3)	19 (5.7)

Table 7c. Treatment-related, treatment-emergent AEs with incidence of $\geq 5\%$ in RFHE3001.

	placebo (n=159)	RFX (n=140)
Any AE, n(%)	127 (79.9)	112 (80.0)
Blood & Lymphatic System	8 (5.0)	15 (10.7)
Anaemia	6 (3.8)	11 (7.9)
Gastrointestinal	67 (42.1)	72 (51.4)
nausea	21 (13.2)	20 (14.3)
ascites	15 (9.4)	16 (11.4)
Abdominal pain	13 (8.2)	12 (8.6)
Abdominal distension	12 (7.5)	11 (7.9)
Constipation	10 (6.3)	9 (6.4)
Abdominal pain upper	8 (5.0)	6 (4.3)
General & Admin. Site	52 (32.7)	56 (40.0)
fatigue	18 (11.3)	17 (12.1)
Oedema peripheral	13 (8.2)	21 (15.0)
pyrexia	5 (3.1)	9 (6.4)
Infections and infestations	49 (30.8)	46 (32.9)
Nasopharyngitis	10 (6.3)	10 (7.1)
Musculoskeletal/Connective Tissue	32 (20.1)	31 (22.1)
Arthralgia	4 (2.5)	9 (6.4)
Muscle spasms	11 (6.9)	13 (9.3)
Back pain	10 (6.3)	9 (6.4)
Nervous System	64 (40.3)	53 (37.9)
Dizziness	13 (8.2)	18 (12.9)
Psychiatric	29 (18.2)	27 (19.3)
insomnia	11 (6.9)	10 (7.1)
Depression	8 (5.0)	10 (7.1)
Respiratory, Thoracic and Mediastinal	39 (24.5)	36 (25.7)
Cough	11 (6.9)	10 (7.1)
Dyspnoea	7 (4.4)	9 (6.4)
Skin and Subcutaneous Tissue	24 (15.1)	29 (20.7)
Pruritus	10 (6.3)	13 (9.3)
Rash	6 (3.8)	7 (5.0)

RFHE3002

A multicentre, open label trial to evaluate the long term safety and tolerability of RFX 550 mg bd in subjects with a history of HE who were randomised into RFHE3001 or were new subjects.

Methods: These were detailed in the sponsor's study report.

Results: the study is ongoing. A total of 267 subjects were enrolled and 208 were active at the time of the interim clinical cut-off (12 February 2009).

Interim analyses

Conn scores and asterixis grades were assessed throughout. Therefore, it was possible to determine time to breakthrough overt HE episode for subjects who completed 6 months of RFX in RFHE3001 and then entered RFHE3002; subjects who received placebo in RFHE3001 and then started RFX in RFHE3002, and in new subjects who started RFX therapy in RFHE3002.

Time to breakthrough overt HE: In subjects who took RFX for up to 680 days (1.9 years), breakthrough overt HE episodes occurred in 72/266 subjects (27.1%) overall: 54/196 subjects (27.6%) in the new RFX group and 18/70 subjects (25.7%) in the continuing RFX group. Time-to-first-breakthrough HE profiles were similar in the RFX group in Study RFHE3001 and the new RFX group in RFHE3002. These data demonstrate that protection against breakthrough overt HE in subjects was consistent between the 2 studies.

Hospitalisations: 124/266 (46.6%) subjects were hospitalised for any cause: 98 in the new RFX group and 35 in the continuing RFX group; a hospitalisation rate of 0.60 event/patient exposure years (PEY). A total of 59 subjects were hospitalized due to HE. Normalising for subject exposure, this represents an HE-caused hospitalisation rate of 0.29 event/PEY.

Conn scores: generally maintained or improved with RFX use up to 18 months. At the last visit, 70.7% of subjects (188/266 subjects) had no change and 20.3% (54/266) had improvements in Conn scores compared with baseline, indicating that mental status was maintained or improved in the majority of subjects (91%) over the treatment period. Like Conn scores, asterixis grades were generally maintained or improved with RFX use up to 18 months. At the last visit, 77.1% of subjects (205/266 subjects) had no change and 16.2% (43/266) had improvements in asterixis scores, indicating that neuromotor symptoms associated with increasing neurological impairment were maintained in 83.3% of subjects over the treatment period. Of the 67 subjects (55 new RFX and 12 continuing RFX) who entered the study with asterixis scores of 1, 2 or 3 (those subjects for whom improvement was possible), 43 subjects (43/67 = 64.2%) showed a 1 (34 subjects; 50.7%), 2 (4 subjects; 6.0%), or 3 grade (5 subjects; 7.5%) improvement from baseline at the last visit recorded for the interim analysis. All subjects were capable of worsening over time and 18/266 subjects (6.8%) did so by 1, 2 or 4 grades; the incidence of worsening asterixis grades were similar between the new (12/196 subjects; 6.1%) and continuing (6/70 subjects; 8.6%) RFX groups. Of the 72 subjects with breakthrough HE in RFHE3002, most had 1 (44 subjects) or 2 (18 subjects) episodes. Ten subjects had 3 or more breakthrough HE episodes in RFHE3002.

Pooled efficacy data for RFHE3001 and RFHE3002 are presented below.

Clinical studies in special populations

There were no studies in special populations that are relevant to this application.

Analysis performed across trials (pooled analyses and meta-analysis)

The all RFX experience, in pooled efficacy analyses of RFHE3001 and 3002 includes data for 337 subjects. In summary:

1. Maintenance or improvement in Conn scores observed for >85% of subjects during RFX treatment for up to 840 days; mean (\pm SD) exposure for all RFX experience was 273.8 (160.92) days. A total of 65.5% of subjects (220/337) had no change in Conn score and 21.1% (71/337) had improvements in Conn score from baseline to last visit;
2. Similarly, maintenance or improvements in asterixis grades were observed for >90% of subjects during RFX treatment. No change from baseline in asterixis grade was reported for 75.2% of subjects (252/337); 17.3% had improvements; Of the 118 subjects who entered the study with a Conn score of ≥ 1 , 62.2% (71/118) showed an improvement from baseline to Conn score 0 at last assessment;
3. Of the 99 subjects who entered with an asterixis grade of ≥ 1 , 58.6% (58/99) showed improvement in asterixis grade from baseline to end of study;
4. Changes from baseline in Conn scores and asterixis grades to last visit were similar among new RFX subjects in RFHE3002, continuing RFX subjects and all RFX experienced subjects (who received RFX in RFHE3001 or in RFHE3002).

Summary: These results support those from RFHE3001 where treatment with RFX was significantly more effective than placebo in the prevention of worsening of Conn score (2.46 times versus placebo, $p = 0.0001$) and in the prevention of worsening of asterixis grade (1.92 times versus placebo, $p = 0.0262$). The similarity between the new and continuing RFX groups in RFHE3002 as well as to the results from the double-blind RFHE3001 shows that with chronic RFX therapy in subjects with a history of HE, Conn scores and asterixis grades are generally maintained or improved over the extended treatment period.

Supportive studies

The open label extension Phase study of RFHE3001, RFHE3002 (above) is ongoing. Safety data from the supportive studies for RFX safety and efficacy in other settings, TD, Pouchitis in UC, IBS, Crohn's disease, are in presented in the *Safety* section.

Evaluator's overall conclusions on clinical efficacy

The pivotal Study RFHE3001 demonstrate that RFX 550 mg bd dosed orally is safe and well tolerated and significantly reduces (by approximately 58%) HE episodes in people with a prior history of HE over 6 months. Accompanying this beneficial effect was a significant reduction in hospitalisation over the 6 months of treatment on study. As almost all subjects on the study were on therapeutic doses of lactulose and remained on lactulose during the study, the study should perhaps be viewed as a study of RFX plus lactulose versus lactulose alone. It is important to recognise that patients randomised to the placebo arm were receiving "standard-of-care therapy" for HE recurrence. The pooled efficacy analyses of RFHE3001 and 3002 provides the largest data set for RFX in this setting ($n=337$) and demonstrates maintenance or improvement in Conn scores with longer exposure to RFX, that is, beyond 6 months.

Safety

Introduction

Patient exposure

Exposure to RFX in the Phase I, II and III program has usually been short term as the majority of studies utilise 3 days treatment with RFX for one of its licensed indications; *the treatment of TD caused by non-invasive strains of E. coli*. So while many thousands of adults and indeed children aged 12 years of older (USA) have been exposed to RFX, this is short term exposure only.

Patient days of exposure in different settings is summarised below:

1. Abdominal Surgery: 1,173;
2. Diarrhoea: 14,710;
3. Hepatic Encephalopathy: 62,352;
4. Other Gi Diseases: 165,730;
5. Pharmacokinetics: 930

In regards to the acute treatment of HE Studies (RFHE9701, RFHE9702, and RFHE9901), exposure to RFX was between 5-14 days. The largest data set for longer exposure comes from the Primary Analysis Populations (RFHE3001 and 3002). Here, all RFX Subjects, Person Years of Exposure (PEY) = 251.9 (N = 336). This includes, subjects newly commenced on RFX, subjects who were randomised to RFX in RFHE3001 and continued into RFHE3002 and subjects randomised to placebo in RFHE3001 who received open label RFX in RFHE3002.

In summary: There is a paucity of long term data for RFX with approximately 252 per years of follow-up.

Adverse events

Phase I, II and III program

Clinical: Treatment Emergent Adverse Events (TEAEs) occurring in at least 2% of RFX treated subjects in the acute treatment phase of the HE studies (RFHE9701, RFHE9702, and RFHE9901) was similar to the percentages of subjects who experienced at least 1 TEAE in the RFX (35.5%), lactitol (28.3%) and placebo (31.1%) treatment groups. In each group the incidence of TEAEs was highest in the GI disorders category. Among RFX treated subjects the most frequently occurring GI disorders were nausea (5.9% versus 2.2% placebo), diarrhoea (3.9% versus 6.7% placebo) and GI haemorrhage (2.6% versus 2.2% placebo).

HE, the indication under study, was recorded as a TEAE for 7 RFX treated subjects (4.6%), 3 lactitol treated subjects (5.7%) and 1 placebo treated subject (2.2%). Other TEAEs occurring in at least 2% subjects who received RFX included pruritus (2.0%), renal failure acute (2.0%) and vomiting (2.0%). Acute renal failure occurred in 3 subjects in the RFX group, 1 subject in the lactitol group and in no subjects treated with placebo. Pruritus occurred in 3 RFX treated subjects and in no subjects treated with lactitol or placebo. All other recorded TEAEs occurred in <3 RFX treated subjects. The incidence of TEAEs was higher in the 600 mg daily dose group (55.6%) and the 2400 mg daily dose group (41.2%) compared with 1200 mg daily group (31.6%). However, the numbers of subjects receiving 600 mg (N=18) or 2400 mg (N=17) daily were small and most reported TEAEs only occurred in 1 subject. The overall pattern of common TEAEs in this population was qualitatively similar to the profile of frequent events in the primary analysis populations.

Table 8. AEs with incidence $\geq 2\%$ among patients receiving RFX tablets, 600 mg/day in placebo controlled studies for TD.

	Number (%) of Patients	
	RFX (N = 320)	Placebo (N = 228)
Flatulence	36 (11%)	45 (20%)
Headache	31 (10%)	21 (9%)
Abdominal Pain NOS	23 (7%)	23 (10%)
Rectal Tenesmus	23 (7%)	20 (9%)
Defecation Urgency	19 (6%)	21 (9%)
Nausea	17 (5%)	19 (8%)
Constipation	12 (4%)	8 (4%)
Pyrexia	10 (3%)	10 (4%)
Vomiting NOS	7 (2%)	4 (2%)

Laboratory values and vital signs: There were no clinically significant mean changes in laboratory values or vital signs during treatment in the Randomised clinical trial (RCT) Study or in the Long Term RFX Experience population. See also Table 7 for a summary of treatment-related, treatment-emergent AEs with incidence $\geq 5\%$ in RFHE3001.

Serious adverse events and deaths

SAE and deaths occurring in the pivotal studies (RFHE3001 & 3002) are summarised in Table 7 and discussed below.

A similar proportion of RFX and placebo treated subjects in the RCT study population experienced severe (26.4%, 30.8%), moderate (37.1%, 34.0%) or mild TEAEs (16.4%, 15.1%), respectively. Severe TEAEs that occurred in $>2\%$ of RFX treated subjects in the RCT study population were as follows (RFX versus placebo): HE (6.4% versus 13.8%), anaemia (2.9% versus 1.3%), abdominal pain (2.9% versus 1.9%), ascites (2.9% versus 1.9%) and oesophageal varices haemorrhage (2.1% versus 1.3%).

Proportions of subjects who had severe, drug related TEAEs were slightly higher in the RFX group (7 of 140) than in the placebo group (4 of 159). The severe, drug related TEAEs in the RFX group were: abdominal pain (1 subject); balance disorder and confusional state (1 subject); dizziness (1 subject); diarrhoea and HE (1 subject); clostridium colitis and HE (1 subject); clostridium colitis (1 subject); and ascites and HE (1 subject).

In the placebo group, severe, drug-related TEAEs were as follows: HE (2 subjects); abdominal pain (1 subject); and nausea (1 subject). With the exception of abdominal pain (placebo subject), all of these events were resolved by last contact. Severe, drug related events of *Clostridium colitis* are discussed below. Both subjects with *C. difficile* had recent clinical histories that included several risk factors for infection.

While a higher percentage of all RFX subjects in the Long term RFX Experience population experienced a severe (41.4%) TEAE compared to the RCT Study groups, after normalising for exposure the event rate for severe TEAEs per 100 PEY in All RFX subjects (55.2) was markedly lower than in the RCT RFX (74.0) and placebo (106.5) groups. Severe TEAEs occurring in ≥ 10 subjects in the Long Term Experience Population (All RFX subjects) were HE (45 subjects), hepatic failure (16 subjects), ascites (13 subjects), renal failure acute (12 subjects) and anaemia (11 subjects). With the exception of hepatic failure, the incidence of these severe TEAEs was comparable between All RFX subjects in the Long Term RFX Experience population and the RFX and placebo treatment arms in the RCT Study. Overall, the profiles of severe TEAEs were generally similar between treatment groups in the RCT Study, with the exception of HE. After normalising for exposure, the majority of severe TEAEs in $\geq 1\%$ of All RFX subjects appeared to decrease in frequency with extended exposure.

Clostridial infections

Twelve cases of *Clostridial* infections were reported cumulatively; 9 were *serious*. No substantial increasing in the rate of incidence of case reports has been observed during postmarketing years: 2 cases (2006); 3 cases (2007); 3 cases (2008); 1 case (2009); 3 cases (2010).

C. Difficile associated diarrhoea/colitis has been observed in patients treated with nearly all antibacterial agents, including RFX. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. Difficile*, which produces toxins A and B responsible for the associated diarrhoea (CDAD). Treatment includes discontinuation of antibiotics that are applying selection pressure for the outgrowth of *C. Difficile* and in cases of severe infection require specific antibiotics. Positive experiences with RFX therapy in patients with CDAD have been reported in literature²⁶ and RFX appears not to disturb the normal colonic flora in contrast with other antibiotics. Nevertheless, CDAD has been associated with RFX use and as such, Clostridial infections have been added into current drug information sheet in countries where the drug is licensed.

Laboratory findings

Clinical laboratory evaluations

The two most frequently occurring post baseline potentially clinically significant (PCS) haematology results in each treatment group were elevated International Normalized Ratio (INR) (>1.7) and decreased lymphocyte percentages (<13.5%). Overall, the trends for subjects with post baseline PCS results in the Long Term RFX Experience population were comparable to findings for each treatment group in the RCT study population.

Similarly, there were few notable mean or median changes in clinical chemistry parameters including liver function tests from baseline to last value or other time points among All RFX subjects in the Long Term RFX Experience population. Findings for mean changes in clinical chemistry parameters were more variable beyond 12 months, numbers very small. Overall, the profiles of shifts for the Long Term RFX Experience population at 3 months, 6 months, 12 months and last value were qualitatively similar to shifts observed in the RCT study population for both the placebo and RFX groups. Moreover, there were few differences in the profiles of shifts at 3, 6 and 12 months for All RFX subjects, indicating that an increase in duration of treatment did not result in noticeable changes to the percentages of subjects who experienced shifts in blood chemistry parameters.

Shifts from normal to high or low at last value in $\geq 10\%$ of All RFX subjects were as follows:

- Lactate dehydrogenase (LDH) was increased as follows: All RFX subjects (16.5%, RCT RFX subjects (17.2%) versus RCT placebo subjects (6.9%);
- ALT was increased from normal at baseline to high at the last assessment in 11.5% of All RFX subjects;
- Alkaline phosphatase was increased from normal at baseline to high in All RFX subjects (12.1%) compared with the RCT placebo group (5.5%);
- Uric acid was increased from normal at baseline to high at the last assessment in 10.9% of subjects;
- Glucose was increased from normal at baseline to high at the last assessment in 12.4% of subjects. No trends over time were noted;
- Gamma GT (GGT) was increased from normal at baseline to high at the last visit in All RFX subjects (10.6%) compared with the RCT placebo group (2.1%);

- Total bilirubin was increased from normal at baseline to high at the last assessment in 10.0% of All RFX subjects. No trends over time were noted and the proportion of subjects with shifts from normal to high in glucose was comparable between All RFX subjects and the RCT Study groups.

Safety in special populations

Intrinsic Factors: The influence of intrinsic factors on the AE profile of RFX in the primary analysis studies (*RFHE3001 and 3002*) examined using race (White, non-White), age (<65, ≥65), sex, baseline hepatic function (MELD score: ≤10, 11-18, or ≥19) and baseline renal function (serum creatinine ≥1.5 times upper limit of normal (ULN) and serum creatinine <1.5 times ULN). For both the RFX and placebo treatment groups the incidence of TEAEs was highest among subjects with a baseline MELD score ≥19 (RFX: 91.7%; placebo:100.0%) and lower among subjects with a baseline MELD score between 11-18 (RFX: 85.1%; placebo:87.5%) and with a baseline MELD score ≤10 (RFX: 61.8%; placebo:58.3%). While the overall incidence of TEAEs during the study was incrementally higher among subjects with more severely impaired hepatic function at baseline, there were no remarkable between-group differences (RFX versus placebo) in the types and frequencies of TEAEs in each MELD score category. The pattern of TEAEs observed in the RCT study population for MELD score subgroups was also observed in the Long Term RFX Experience population. As in the RCT Study groups, a correlation was observed between increasing MELD scores and a higher incidence of TEAEs. No dose modifications are recommended for patients based on the analysis of hepatic function (see below).

Hepatic Impairment: Systemic exposure of RFX was approximately 10, 13 and 20 fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to healthy volunteers. No dosage adjustment is recommended because RFX is nevertheless even in this setting very poorly systemically absorbed;

Renal impairment; no data available but due to the PK profile none expected;

Elderly: In the controlled trial of RFX 550 mg for HE, 19.4% were 65 and over, while 2.3% were ≥75. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, although numbers were small;

Gender and Race: no differences in safety profile have been revealed by gender or race;

Paediatric: Not studied in children <12 years (TD indication); no data in HE;

Pregnancy: safety in pregnancy unknown; teratogenicity in some animal species at doses between 2-5 times the doses for TD/HE;

Breastfeeding: No data on excretion of RFX into breast milk; safety is unknown.

Immunological events

None revealed.

Safety related to drug-drug interactions and other interactions

In vitro and *in vivo* data described under *Pharmacokinetics* did not suggest and clinically meaningful safety signal is likely with RFX.

Discontinuation due to Adverse Events

This is summarised in Table 7 for the pivotal Study RFHE3001. Discontinuation for AE were similar between the RFX and placebo arms.

Postmarketing experience

The report provided covered the period from 23 April 1985 (date of first international authorisation of RFX) to 15 November 2010. The current submission included all safety information, that is, spontaneous reports medically comprising a total of *425 case reports* (229 spontaneous medically confirmed cases, 7 cases from literature, 184 case reports from consumers, and 5 Suspected Unexpected Serious Adverse Reaction (SUSARs) from clinical trials performed on new formulations of RFX: 400 mg EIR-tablet and 550 mg film-coated tablet). In total, there were 40 medically confirmed serious unlisted cases. Two cases with fatal outcome received during this overall reporting period. In none of them the case assessment provided any evidence of certain causal relationship with RFX. The product information has been updated; current version November 2010.

During post approval use of RFX further AEs have been reported. The frequency of these reactions is not known as it cannot be estimated from the available data: Infections and infestations: Clostridial infections; Blood and lymphatic system disorder: Thrombocytopenia; Immune system disorders: Anaphylactic responses, Angioedemas, Hypersensitivity; Nervous system disorders: Presyncope, Syncope; Hepatobiliary disorders: Liver function tests abnormalities; Skin and subcutaneous tissue disorders: Dermatitis, Eczema, Erythemas, Pruritus NEC, Purpura, Urticarias; Investigations: INR abnormalities.

List of questions

Pharmacokinetics

Is there any data for the co-administration of rifampicin and RFX, increasingly rifampicin is being utilised as an antibiotic for Methicillin resistant *Staphylococcus aureus*.

Safety

There is a relative paucity of data for chronic exposure. It will be important to monitor the emergence of secondary infections (*Clostridia*) or other resistant gut organisms with chronic use, including *Vancomycin resistant enterococci* (VRE). Postmarketing reporting in this regard should be encouraged.

Clinical summary and conclusions

Pharmacokinetics:

Absorption: <1% of the oral dose is absorbed; food increases absorption marginally; the drug can be dosed fasted or fed;

Distribution: very poor oral bioavailability; of the <1% drug absorbed, moderate (approximately 65%) plasma protein bound;

Metabolism: of the small amount of drug absorbed, metabolised (enzyme pathway unknown);

Elimination: 97% eliminated unchanged in faeces; biliary excretion of drug that is absorbed; minimal renal excretion of metabolites (0.32%) and unchanged drug (0.03%).

Special Populations: No dose reductions in those with hepatic impairment despite the fact that systemic levels (AUC) are higher, systemic levels are still very low.

Drug-drug interactions: There is very little potential for drug-drug interactions especially as RFX has such poor systemic absorption. *In vitro* studies have shown that RFX did not inhibit CYP isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging from 2 to 200 ng/mL. RFX is not expected to inhibit these enzymes in clinical use.

An *in vitro* study has suggested that RFX induces CYP3A4. However, in patients with normal liver function, RFX at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether RFX can have a significant effect on the PK of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated RFX concentrations. *In vivo* studies of interactions with MDZ and OCP show minimal interactions, although the PI lists caution when co-administration of OCP especially if the dose of EE is <.

Pharmacodynamics

RFX, an orally administered rifamycin antibiotic, is very poorly absorbed and works at the luminal level of the GI tract to reduce the by-products (nitrogenous waste including ammonia products) of the gut flora. These nitrogenous products of bacterial metabolism that are thought to contribute to the development of and recurrence of HE in those with liver cirrhosis. However, clinical benefit in terms of scoring of HE severity and/or reduction in HE recurrence across a wide range of RFX doses, most studied is 1200 mg/day, with proven reductions in faecal flora burden. However, inconsistent reductions in venous ammonia levels with RFX versus placebo.

Dose-response studies and main clinical studies

The pivotal studies demonstrate that RFX 550mg bd orally results in a 57.9% reduction, when compared with placebo, in the risk of experiencing breakthrough overt HE during the course of this study in adults with a history of HE. It is noteworthy that more than 90% of subjects were receiving lactulose at baseline and remained on this agent during the study. The open label study RFHE3002 is ongoing but interim analyses demonstrate similar efficacy to the double blind placebo controlled phase of the study (RFHE3001).

Ancillary analyses

None, aside from a PK substudy of RFHE3001 which confirmed the findings of the Phase 1 PK programme.

Analysis performed across trials (pooled analyses AND meta-analysis)

Pooled efficacy (and safety data) from the pivotal chronic exposure studies in HE confirm the findings of the double-blind placebo controlled phase; moreover these data confirm an ongoing benefit of RFX beyond the 6 months of the initial RCT trial in the prevention of HE recurrence.

Supportive studies

Data from the studies in TD, UC-related pouchitis, Crohn's disease, IBS were included. Exposure in these settings was short, for the most part 3 days (for TD). Provides additional safety data for the indication but most exposures in these settings were short.

Clinical safety

Patient exposure

In the chronic setting, there is a paucity of long term safety data; 252 per years of follow-up. No safety signal of concern has emerged. The post marketing experience includes >100,000 patient *days* of exposure.

Adverse events

No safety signal of note, in the postmarketing phase, the following has been reported and the PI updated; current November 2010.

Infections and infestations: Clostridial infections; Blood and lymphatic system disorder: Thrombocytopenia; Immune system disorders: Anaphylactic responses, Angioedemas, Hypersensitivity; Nervous system disorders: Presyncope, Syncope; Hepatobiliary disorders: Liver function tests abnormalities; Skin and subcutaneous tissue disorders:

Dermatitis, Eczema, Erythemas, Pruritus NEC, Purpura, Urticarias; Investigations: INR abnormalities

Dose modification because of adverse events

Not applicable, discontinuations in the RFX groups equivalent or fewer than placebo. Drug well tolerated.

Serious adverse events and deaths

In the chronic exposure HE studies, none reported as related to RFX.

In summary: There is no safety signal of concern in the clinical program for RFX in the setting of HE or other conditions for which it has received licensure in many countries, that is, TD. Incidence of *Clostridia* infections is very low but should be monitored when this drug is used chronically as per all antibiotics that are administered chronically.

Laboratory findings

No laboratory signal of concern.

Safety in special populations

No concerns. No data in the setting of renal impairment. Caution in the setting of severe hepatic impairment; systemic absorption increased but unclear whether this is associated with a clinical/safety consequences and levels of the drug are still very low in this setting and no dose adjustment is recommended.

Immunological events

None reported.

Safety related to drug-drug interactions and other interactions

The Combined OCP can be administered with RFX without dose adjustment although the PI recommends caution and the use of another contraceptive method when women are taking an OCP which contains <50 µg of EE. Note that there is no PK data on the OCP when co-administered with the RFX 550 mg bd dose.

Discontinuation due to adverse events

Minimal, and equivalent to placebo.

Benefit risk assessment

This is a full application for the registration of rifaximin, a poorly absorbed antibiotic of the rifamycin family, dosed at 550 mg bd for the prevention of recurrence of HE in adults. HE episodes occur on the background of end-stage liver disease (cirrhosis or non-cirrhotic portal hypertension). The benefits of this drug have been demonstrated in a randomised clinical trial; the benefits outweigh the risk. The evaluator recommended that this drug be approved in this setting.

Benefits

In favour of RFX in terms of clinical efficacy in this setting and quality of life (reduction in hospital admission); the drug appears safe and well tolerated.

Risks

Minimal compared to the benefits. The drug is a poorly absorbed oral administered antibiotic and could be viewed as a topical agent working at the level of gut lumina. Poor systemic absorption accounts for low rates of adverse events and accounts for differences between this drug and other drugs in this class such as rifampicin.

Balance

Favours RFX.

Conclusions

Conditions for registration

The evaluator considered these data presented in the application as robust enough to recommend that RFX is registered as a treatment for the prevention of HE recurrence in adults ≥ 18 years of age.

V. Pharmacovigilance findings

Risk management plan

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

Safety Specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 9. Subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 9. Summary of Ongoing Safety Concerns

Safety concern	Planned actions
1. Clostridial infections	Labelling: Warnings included in Product Information "Precautions" and CMI. Routine pharmacovigilance
2. Allergic reactions	Labelling: Contra-indicated in patients with hypersensitivity to any of the rifamycin antimicrobial agents in the PI and CMI states "Before you take XIFAXAN" etc Routine pharmacovigilance
3. Potential for new drug-drug interactions	Safety signal detection. Follow-up in PSUR
4. Potential off-label use: Prevention of the recurrence of hepatic encephalopathy in adults	Labelling: Warnings in Product Information "Section Precautions" and CMI "Section What XIFAXAN is used for" and "Section Before you take XIFAXAN" Routine pharmacovigilance to monitor for reports of off-label use. Follow-up in PSUR
5. Potential off-label paediatric use: Rifaximin is proposed for the prevention of the recurrence of hepatic encephalopathy in adults	Labelling: Warnings in Product Information "Section PRECAUTIONS Paediatric Use" and CMI "Section Before you take XIFAXAN -Before you start to take it" Routine pharmacovigilance to monitor for reports of off-label use. Follow-up in PSUR

OPR reviewer comment

Pursuant to the evaluation of the clinical aspects of the SS, it is recommended that the following Important missing information be included as Ongoing Safety Concerns:

- Patients with severe hepatic impairment

- Patients with impaired renal function
- Pregnant and lactating women
- Paediatric patients
- Long term use

In addition the clinical evaluator indicates that the Important potential risk: 'Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)' should also be included as an Ongoing Safety Concern.

The relevant sections of the RMP should be amended accordingly.

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities, consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, to monitor all the specified Ongoing Safety Concerns.

Furthermore the initial RMP proposed to further monitor the Important potential risk: 'Potential for new drug-drug interactions' by conducting a Post authorisation drug utilisation trial to calculate the incidence of co-administration of rifaximin with other drugs and by applying "*continuous and close monitoring of safety signals deriving from post-marketing data*". However, no details of these additional pharmacovigilance activities were provided in the RMP.

Subsequently the sponsor's correspondence of 1 June 2011 advised:

"The risk management plan (RMP) submitted to the TGA contained an error in Table 23. We do not propose to conduct an additional post-authorisation drug utilisation trial."

and

"Safety signals in the post-marketing phase will be captured by routine pharmacovigilance activity and no additional activities are judged necessary. Reference to additional risk minimisation measure(s) should therefore have been deleted from the Risk Management Plan."

In the sponsor's correspondence dated 4 January 2012, it was stated that this post authorisation drug utilisation study was requested by the United Kingdom (UK) regulatory agency⁴⁷ during its review of a national marketing authorisation application for rifaximin 200 mg tablets for use in the treatment of traveller's diarrhoea. Reference to this study was deleted from the revised RMP submitted with this correspondence. The sponsor also provided an assurance that no similar post authorisation studies in the indication of hepatic encephalopathy are planned in any markets.

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

Routine pharmacovigilance activities should also be used to monitor the following new Ongoing Safety Concerns:

- Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)

⁴⁷ Medicines and Healthcare Products Regulatory Agency (MHRA)

- Patients with severe hepatic impairment
- Patients with impaired renal function
- Pregnant and lactating women
- Paediatric patients
- Long term use

The sponsor should amend the PP of the RMP accordingly.

Risk minimisation activities

Routine risk minimisation activities will include indications, contra indications, precautionary statements and/or notification of undesirable effects in the Australian PI for all the specified Ongoing Safety Concerns.

In addition it is acknowledged that routine risk minimisation activities have already been proposed for:

- Patients with severe hepatic impairment
- Patients with impaired renal function
- Pregnant and lactating women
- Paediatric patients

OPR reviewer comment

The sponsor's proposed use of routine risk minimisation activities would appear to be reasonable, except for the absence of any such activity for the new Important potential risk: 'Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)' and the new Important missing information: 'Long term use'. Consequently Table 21; 'Summary of safety concern and risk minimisation measures' and Table 22; 'Summary of risk minimisation plan' should be amended to incorporate the following new Ongoing Safety Concerns:

- Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)
- Patients with severe hepatic impairment
- Patients with impaired renal function
- Pregnant and lactating women
- Paediatric patients
- Long term use

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- The sponsor should ensure that appropriate version control is applied to future revisions of the RMP for this medicine.

- It is recommended that the following Important missing information be included as Ongoing Safety Concerns and the relevant sections of the RMP should be amended accordingly:
 - Patients with severe hepatic impairment
 - Patients with impaired renal function
 - Pregnant and lactating women
 - Paediatric patients
 - Long term use
- It is recommended that the Important potential risk: 'Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)' should be included as an Ongoing Safety Concern. The relevant sections of the RMP should be amended accordingly.
- Routine pharmacovigilance activities should be used to monitor the new Ongoing Safety Concerns.
- The sponsor's justification and conclusion that routine risk minimisation is sufficient at this stage for all the specified Ongoing Safety Concerns would appear to be reasonable.
- New information provided in the sponsor's correspondence dated 4 January 2012, relating to the 'Potential for medication errors' section of the RMP should be incorporated into this part of the RMP when it is next updated.
- The sponsor's proposed use of routine risk minimisation activities would appear to be reasonable, except for the absence of any such activity for the new Important potential risk: 'Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)' and the new Important missing information: 'Long term use'. Consequently Table 21; 'Summary of safety concern and risk minimisation measures' and Table 22; 'Summary of risk minimisation plan' should be amended to incorporate the following new ongoing safety concerns:
 - Other resistant gut organism infections, including *Vancomycin resistant enterococci* (VRE)
 - Patients with severe hepatic impairment
 - Patients with impaired renal function
 - Pregnant and lactating women
 - Paediatric patients
 - Long term use
- In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft PI and consumer medicine information (CMI) documents also be revised, the details of the proposed revisions are however beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no pharmaceutical objections to registration of Xifaxan. The evaluator considered the data support a shelf-life of 12 months at below 25°C. The sponsor had proposed 3 years below 25°C based on results of 3 batches that demonstrated compliance with specifications during 2 years storage at 25°C/60% rh. However, the evaluator noted a consistent and significant decrease in potency of the product under those storage conditions and statistical analysis of the data indicated that a shelf-life of only 12 months is warranted. This submission was considered at the 142nd PSC meeting in November 2011.

Rifaximin is a semisynthetic antibiotic derived from the fermentation product, RifamycinSV. Rifaximin contains 9 asymmetric carbon atoms. The fermentation process fixes the stereochemistry at all 9 asymmetric carbons and no epimerisation occurs during subsequent synthetic transformations. Five crystalline polymorphic forms of rifaximin have been isolated however only rifaximin α is obtained from the manufacturing procedure and is verified in the proposed drug substance specification using x-ray diffraction techniques. This is important as forms γ and δ have significant systemic absorption. Rifaximin was developed over 20 years ago and at that time polymorphism was not known. The sponsor has provided evidence that the alpha form does not convert into other polymorphic forms during manufacture or storage of Xifaxan tablets.

Nonclinical

There were no nonclinical objections to registration. The main nonclinical issue was the very modest exposures achieved in animal studies compared to clinical exposure in patients with impaired liver function. A secondary issue was the apparent hepatotoxicity reported in earlier non-GLP repeat dose toxicity studies in rats and dogs, not reproduced at higher doses in the more recent GLP studies. Those concerns prompted the FDA to require the postmarketing conduct of a chronic, oral, nonclinical toxicology study with achieved AUC exposures comparable to the highest AUCs observed in patients with cirrhosis of the liver. This study is to be reported to the FDA by June 2013. The nonclinical evaluator has recommended this report also be submitted to the TGA as a condition of registration.

Nonclinical kinetic data for rifaximin were limited due to the low levels of GI absorption in animals. *In vitro* studies confirmed a high activity of rifaximin against a range of anaerobic bacteria of faecal flora as well as against enteropathogens producing traveller's 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 well below the clinical exposure. Rifaximin does not enhance cross-resistance to rifampicin against *Mycobacterium tuberculosis*.

Rifaximin had no adverse effects on the CNS, cardiovascular system, respiratory system or renal function at estimated exposures several times the clinical exposure. *In vitro* there was no potential to induce QT interval prolongation at concentrations several orders of magnitude above the clinical exposure. Rifaximin had no effect on gastric motility/secretion and no evidence of GI damage at those exposure levels.

General toxicity was examined in rats, mice and dogs. Acute toxicity was very low with signs of toxicity attributed to the vehicle only. On repeat dosing there was no clear treatment related toxicity in mice, rats showed reduced body weight and non-specific toxicity at 300 mg/kg/day (fully reversible) and in dogs there was reduced body weight and thymus weight at 100 mg/kg/day. There was no evidence of genotoxicity in *in vitro* studies. In a 2 year oral carcinogenicity study in rats there was a non significant trend in

males for malignant schwannomas in the heart at a HD incidence (5%) exceeding historical control (1.7%) with exposure estimated at twice clinical exposure. There was no evidence of carcinogenicity in a 6 month oral study in transgenic mice at plasma exposure 2 to 4 times the clinical C_{max} in healthy volunteers but less than C_{max} in patients with hepatic impairment.

Clinical

Pharmacology

Rifaximin is not intended to be absorbed but rather to act within the GIT. It has very low systemic bioavailability and hence plasma levels could not reliably be detected in several of the PK studies. There was considerable inter-patient variability in PK but absorption was so low this would not be clinically relevant.

Following a single 400 mg ^{14}C - rifaximin dose in healthy subjects, >96% of total radioactivity was present in the faeces and 0.32% was recovered in urine mostly as metabolites with 0.03% as unchanged drug. Rifaximin accounted for 18% of radioactivity in plasma. These data suggest that the small percentage of rifaximin absorbed undergoes metabolism but the enzymes responsible are unknown. In a separate study rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of rifaximin.

There was no absolute bioavailability study because this medicine is not intended for systemic action. Administration of rifaximin 550 mg as a single dose or as multiple dose bd or td regimens resulted in mean AUC values of 11.1 ng.h/mL ($AUC_{0-\infty}$), 12.3 ng.h/mL (AUC_{tau} , steady state), and 9.3 ng.h/mL (AUC_{tau} , steady-state), respectively. No significant accumulation occurred on multiple dosing. In healthy subjects food delays rifaximin absorption with mean T_{max} increasing from 0.75 (fasting) to 1.5 hours (fed) and increases the drug's systemic exposure after single 550 mg doses by approximately 2-fold (from 11.1 to 22.5 ng.h/mL).

In subjects with impaired liver function given rifaximin 550 mg bd, AUC_{tau} at steady-state in subjects with Child-Pugh A and B were approximately 9.6 and 13.1 fold higher, respectively, than in healthy subjects at steady-state. A positive correlation between baseline ALT and maximum plasma concentration (C_{max}) was also observed. The terminal $t_{1/2}$ of rifaximin was significantly longer (about 2 fold) in HE subjects versus healthy subjects. This higher exposure found in subjects with HE may be due to a reduction in the systemic clearance of the drug perhaps because of portal-systemic shunts. Systemic bioavailability remained low.

Rifaximin did not have clinically significant effects on QT interval and drug interactions due to effects on CYP isoenzymes or p-glycoprotein.

Rifaximin has a broad spectrum of activity against many non-invasive GI pathogens and normal faecal flora. Variable schedules of oral dosing achieve very high levels of intra-luminal rifaximin well above the MIC50 and MIC90 for most of these organisms. There appears to be little to no selection of resistance although most data is derived from relatively short-term exposure to rifaximin, that is, in the setting of treatment or prevention of traveller's diarrhoea.

Efficacy

The proposed 1100 mg/day dose given as 550 mg bd was chosen for the pivotal studies (3001 and its open label extension 3002) based on results showing the effectiveness of rifaximin 1200 mg/day (2x200 mg tablets td) in patients with HE in the chronic setting,

pilot studies in HE, assessment of the transit time of rifaximin in healthy adults and from studies of rifaximin performed for other indications including traveller's diarrhoea, Crohn's disease, and ulcerative colitis.

Study 3001 was a randomised, multi centre, double blind, placebo controlled study to evaluate the efficacy, safety and tolerability of rifaximin 550 mg bd for 6 months in preventing HE. The primary objective was to compare the maintenance of remission from previously demonstrated recurrent, overt, episodic HE as measured by Conn score and asterixis grade during 6 months of treatment with rifaximin at 550 mg bd or placebo. The secondary objectives were to compare the safety, tolerability and quality of life (QoL) measurements using long term dosing with rifaximin compared to placebo in the maintenance of remission from HE.

The primary endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as an increase of Conn score to Grade ≥ 2 (0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. Time to breakthrough overt HE episode was the duration from time of first dose of study drug to the first breakthrough overt HE episode. Subjects were withdrawn from study on experiencing an overt HE episode. Subjects who completed the study and did not experience a breakthrough overt HE episode were censored at the time of their 6 month visit. Subjects who terminated early for reasons other than breakthrough overt HE were contacted at 6 months from randomisation to determine if they'd experienced a breakthrough overt HE episode or other outcome (mortality status). If a subject had not experienced a breakthrough overt HE event prior to contact that subject was censored at the time of contact. This method was intended to capture all breakthrough overt HE episodes up to 6 months post-randomisation.

Key secondary endpoints were:

- Time to first HE-related hospitalisation.
- Time to any increase from baseline in Conn score (mental state grade).
- Time to any increase from baseline in asterixis grade.
- Mean change from baseline in fatigue domain score on the CLDQ at end of treatment.
- Mean change from baseline in venous ammonia concentration at end of treatment.

A total of 299 subjects were enrolled. Median age was 56.0 years (range, 21-82 years) and 19.4% of subjects were ≥ 65 years of age. Some 86% were White and 60.9% were male. All subjects had a history of overt, episodic HE associated with advanced liver disease that was diagnosed by evidence of ≥ 2 episodes of overt HE (Conn score of ≥ 2) within 6 months prior to screening. At the baseline assessment subjects were in remission with a Conn score of 0 or 1. Baseline Conn score was 0 for 66.9% of subjects and 1 for 33.1% of subjects. Most subjects had asterixis Grade 0 (68.2%) or Grade 1 (28.8%).

The mean (\pm SD) duration of current verified remission from HE (time since the most recent verified HE event) was 71.1 (± 49.62) days; most subjects had experienced 2 (69.6%) or 3 (21.4%) episodes of HE during the 6-month interval prior to study entry. Most (91.3%) subjects received lactulose as a prior medication *and* as a concomitant medication during the study. The percentages taking lactulose and the mean quantity taken were similar in both groups. Mean (\pm SD) daily lactulose use was 3.14 (± 2.096) cups/day in the rifaximin group and 3.51 (± 2.592) cups/day in the placebo group. (NB: One cup of lactulose is equal to 15 mL [10g lactulose/15 mL]).

Breakthrough overt HE episodes occurred in 31/140 (22%) subjects given rifaximin and in 73/159 (45.9%) given placebo during the 6 month period since randomisation (up to Day 170). Comparison of Kaplan-Meier estimates of time to breakthrough overt HE

between groups showed a highly significant protective effect of rifaximin ($p < 0.0001$). The HR for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the risk in the placebo group was 0.421 (95% CI: 0.276 to 0.641) during the 6 month treatment period, that is, rifaximin reduced the risk of experiencing breakthrough overt HE of ~58%.

Subjects who didn't experience breakthrough overt HE were followed after study discontinuation and the primary efficacy endpoint was analysed up to last contact. Results were similar to the analysis of the 6-month treatment period, that is, a total of 34/140 subjects in the rifaximin group and 73/159 subjects in the placebo group had breakthrough overt HE during the Treatment Period **plus follow-up**; HR 0.461 (CI: 0.307 to 0.693) ($p = 0.0001$).

Strong independent predictors of breakthrough overt HE episodes were: age at baseline ($p=0.0160$); MELD score ($p=0.0003$); duration of current verified remission ($p=0.1089$); and number of prior HE episodes ($p=0.0022$). To control for these factors on outcome due to chance imbalances between treatment groups, multivariate analysis was performed using the Cox proportional hazards model including treatment group, age, MELD score, duration of current verified remission and number of prior HE episodes. The hazard ratio (rifaximin: placebo) was 0.403 (95% CI: 0.264 to 0.617) ($p < 0.0001$). These data show that rifaximin treatment results in a ~60% reduction versus placebo in the risk of experiencing a breakthrough overt HE episode when independent predictors are controlled. The most influential prognostic factors in the multivariate analysis were age ($p = 0.0225$) and baseline MELD score ($p = 0.0005$).

There were statistically significant differences in hospitalisation rates due to HE and risk of experiencing an increase in CONN score both favouring rifaximin and a trend towards higher asterixis grade and higher venous ammonia levels in subjects given placebo versus rifaximin.

Study 3002 was a multicentre, open label study to evaluate the long-term safety and tolerability of rifaximin 550 mg bd in subjects with a history of hepatic encephalopathy who were randomised into Study 3001 or were new subjects. The study was ongoing at the time of preparation of this submission and interim data from 267 subjects were presented. In subjects who took rifaximin for up to 680 days (1.9 years) breakthrough overt HE episodes occurred in 72/266 subjects (27.1%) overall: 54/196 subjects (27.6%) in the new rifaximin group and 18/70 subjects (25.7%) in the continuing rifaximin group. Time-to-first-breakthrough HE profiles were similar between the rifaximin group in Study 3001 and the new rifaximin group in Study 3002.

Results of Studies 3001 and 3001 were pooled to assess long term efficacy outcomes. In the pooled dataset, maintenance or improvement in Conn scores observed for >85% of subjects during rifaximin treatment for up to 840 days. Mean (\pm SD) exposure for all rifaximin experience was 273.8 (160.92) days.

A total of 65.5% of subjects (220/337) had no change in Conn score and 21.1% (71/337) had improvements in Conn score from baseline to last visit. Maintenance or improvement in asterixis grade were observed for >90% of subjects during rifaximin treatment. No change from baseline in asterixis grade was reported for 75.2% of subjects (252/337) and 17.3% had improvements.

Safety

While many individuals have received short courses of rifaximin, including in the pharmacology studies in this submission, the proposed indication requires long term exposure. Safety analyses were presented for the placebo controlled period and for the pooled 3001 and 3002 safety populations. Mean (\pm SD) exposure for all rifaximin subjects (550 mg bd) in the Long Term Rifaximin Experience population was 273.8 (160.92) days;

median (minimum, maximum) exposure was 253.0 (7, 840) days. Combined data represent approximately 252 person-years to rifaximin 550 mg tablets bd in the primary analysis studies. In total 114 subjects received rifaximin at the proposed dose for at least 12 months and 182 received rifaximin for at least 9 months.

Overall, in Study 3001 the pattern of treatment emergent adverse events (TEAEs) in the rifaximin group was similar to the placebo group with TEAEs occurring in 80% of subjects in each group. Severe TEAEs (31% versus 26%), drug-related TEAEs (21% versus 19%), SAEs (40% versus 36%), and TEAEs leading to discontinuation (28% versus 21%) all occurred at a higher rate in the placebo group compared with the rifaximin group.

In rifaximin treated subjects in Study 3001, TEAEs occurring in at least 10% of the rifaximin group were: peripheral oedema (15.0% versus 8.2% placebo); nausea (14.3% versus 13.2%); dizziness (12.9% versus 8.2%); fatigue (12.1% versus 11.3%); ascites (11.4% versus 9.4%); diarrhoea (10.7% versus 13.2%); and headache (10.0% versus 10.7%). HE episodes that satisfied protocol defined criteria for a SAE (such as requiring hospitalisation) occurred in 12.1% of subjects given rifaximin versus 21.4% of subjects given placebo.

The incidence of AEs in the Long Term Rifaximin Experience population (Studies 3001 and 3002 combined) was comparable to the respective treatment groups in Study 3001. For all rifaximin treated subjects in the primary analysis studies, the most frequent TEAEs were: peripheral oedema (18.2%); nausea (15.8%); ascites (13.1%); urinary tract infections (12.2%); abdominal pain (11.9%); fatigue (11.3%); diarrhoea (10.7%); muscle spasms (10.4%); and dizziness (10.1%).

In Study 3001, serious TEAEs were experienced by a comparable proportion of subjects in the rifaximin group (36.4%) and the placebo group (39.6%). More frequently reported serious TEAEs experienced by rifaximin-treated subjects in Study 3001 were: HE (n=16); anaemia (n=4), ascites (n=4), oesophageal varices haemorrhage (n=4), and pneumonia (n=4). The incidences of SAEs of anaemia (2.9% versus 0%), oesophageal varices haemorrhage (2.9% vs. 1.3%), pneumonia (2.9% versus 0.6%) and vomiting (2.1% versus 0%) were at least 2 fold higher in the rifaximin group compared with the placebo group. The SAEs of anaemia had onset dates at various times after the start of rifaximin therapy (51 to 112 days). These subjects tended to have mitigating causal factors, including acute blood loss related to oesophageal variceal bleeding, longstanding medical history of anaemia associated with chronic disease and fluid overload secondary to low albumin. All of the SAEs resolved with intervention and were assessed as not related to study drug by the reporting investigator. Of note, a higher proportion of rifaximin treated subjects had a medical history of anaemia (30.7%) in Study 3001 rifaximin group compared with placebo treated subjects (17%).

There were 21 deaths during or within 30 days following the last dose in Study 3001, eleven subjects (6.9%) in the placebo group and 10 subjects (7.1%) in the rifaximin group. Of the recorded deaths in Study 3001, twelve occurred (rifaximin: 6; placebo: 6) while receiving study drug, including through to 5 days after last dose. None of these deaths were considered by the study investigator to be related to study drug. A further 23 subjects died during or within 30 days after the last dose in Study 3002. Three additional subjects died in Study 3002 after completion of the planned interval for collection of SAEs (up to 30 days after last dose of the study drug). A total of 13 subjects died while receiving study drug in Study 3002 (including through to 5 days after last dose). In both Studies 3001 and 3002 no deaths were judged by the assessing investigator as related to study drug. The majority of subject deaths appear to be associated with deteriorating hepatic function and underlying disease progression (sponsor's Clinical Overview).

Risk management plan

The RMP evaluator considered the RMP supportive to the application and recommended that implementation of a RMP satisfactory to the TGA be a condition of registration. The following were considered important Ongoing Safety Concerns: patients with severe hepatic impairment; patients with impaired renal function; pregnant and lactation women; paediatric patients; and long term use.

The evaluator also recommended that the Important potential risk “Other resistant gut organism infections including *Vancomycin resistant enterococci* (VRE)” be included as an Ongoing Safety Concern.

The sponsor has proposed routine risk minimisation activities and the evaluator considered this adequate except for the need for greater assessment of the risk of development of other resistant gut organism infections including *Vancomycin resistant enterococci* (VRE).

Risk-benefit analysis

Delegate considerations

Efficacy of rifaximin in combination with lactulose in the prevention of recurrence of hepatic encephalopathy has been very clearly demonstrated in the data presented. Not only were recurrences of overt HE reduced but associated symptoms including mental status, assessed using Conn’s grading scale and asterixis were also reduced. The major issue regarding efficacy is that any indication for treatment of HE should reflect the patient population in whom efficacy has been demonstrated. As over 90% of patients received rifaximin concurrently with lactulose, consideration could be given to limiting the indication to adjunctive treatment with lactulose but the Delegate considered this would be overly restrictive and would prevent access for those patients who were intolerant of or otherwise unable to take lactulose.

The adverse events seen in the pivotal studies, including the deaths were reflective of the study population. Although there was an increase in anaemia related AEs in subjects given rifaximin those subjects had a higher incidence of anaemia at baseline compared with subjects given placebo. The number of subjects given rifaximin for at least 12 months is acceptable. Even for non life threatening conditions current guidelines indicate data from 100 individuals treated for at least 12 months is the minimum number that is acceptable.

While the clinical studies were performed only in adults the Delegate did not consider that it was necessary for the indication to specify that this product should be used in only in adults. It is sufficient to state in the *Use in Children* section of the PI that there are no data on the safety and efficacy of rifaximin in the prevention of recurrence of HE in children or adolescents.

Conclusion and recommendation

The Delegate proposed to approve Xifaxan for;

Prevention of the recurrence of hepatic encephalopathy.

Registration was to be subject to submission of a revised Risk Management Plan that is acceptable to the Office of Product Review.

The advice of the ACPM is specifically requested on whether the indication should be restricted to concurrent use with lactulose and/or to use in adults only.

Response from sponsor

Norgine agreed with the proposed actions of the Delegate that Xifaxan 550 mg tablets should be approved for the "*Prevention of the recurrence of hepatic encephalopathy.*"

The original indication applied for was "*Prevention of the recurrence of hepatic encephalopathy in adults*". The sponsor noted the Delegates proposal to remove the words "*in adults*" from the indication and had no objection to this. While the incidence of hepatic encephalopathy in children is very rare, the sponsor believed that use in children should not be specifically excluded from the indication, provided that the PI makes clear the limitations of safety and efficacy data in children. The sponsor noted a recently published anecdotal report of successful use of rifaximin to treat hepatic encephalopathy in a child.⁴⁸

The clinical evaluator noted that in the pivotal clinical study, RFHE3001, Xifaxan was safe and well tolerated and significantly reduced episodes of hepatic encephalopathy ($P < 0.001$), as well as significantly reducing episodes of hospitalisation ($P = 0.01$) over the 6 months of the study. The open label extension study showed that this benefit was maintained.

Norgine was also in agreement with the proposal of the Delegate that the indication should not be restricted to adjunctive treatment with lactulose, as this would prevent use of Xifaxan in those patients who are intolerant to lactulose, or in whom lactulose is contraindicated. A statement that Xifaxan was used in conjunction with lactulose in 91 % of the patients in the pivotal clinical study is included in both the *Clinical Trials* and *Dosage and Administration* sections of the PI and the sponsor believed that this is sufficient in disclosing the patient population in whom clinical efficacy has been established.

Norgine acknowledged that there may be concerns about the potential for development of bacterial resistance to rifaximin. However, due to its very low level of absorption from the gastro-intestinal tract, rifaximin acts locally in the intestinal lumen and has no effects on systemic invasive pathogens. For the same reasons Norgine believes that the development of clinically significant microbial resistance will be very unlikely and has not been reported as a clinical problem following the use of rifaximin for hepatic encephalopathy or during its much longer period of use (over 20 years) in the treatment of traveller's diarrhoea and other indications. The potential for the development of resistant organism infections, including Vancomycin resistant enterococci (VRE) has been added to the summary of safety concerns in the Xifaxan Risk Management Plan.

The mechanism for the development of resistance to rifaximin, is a chromosomal onestep 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.

Advisory committee considerations

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

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

In adults, secondary prevention of recurrence of hepatic encephalopathy following at least two previous overt episodes that are not due to gastrointestinal bleeding,

⁴⁸Malia T et al (2011). Rifaximin or hepatic encephalopathy in children : Case report. Arch Argent Pediatr 109: 113-5

sedative use or primary central nervous system disease, where other treatments are contraindicated or have failed.

In making the recommendation the ACPM expressed specific concern about the risk of *Clostridium difficile* infection and rifampicin resistance in *Staphylococcus aureus* carriers, specifically in view of the long term use of this product in patients frequently in institutionalised care.

The ACPM agreed with the Delegate's proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on inclusion of the following:

- A statement in the *Precautions section* of the PI to ensure accurate reflection of the risk of resistance. This should also be reflected in the CMI.
- A statement in the *Dosage and Administration section* of the PI to recommend dosage reduction following bleeding control.
- A statement in the *Dosage and Administration* and *Clinical Trial* sections of the PI to ensure prescriber awareness of the limitations of safety and efficacy data in children including sufficient pharmacokinetic data to guide dosing in children.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- The Risk Management Plan to require vigilance and reporting particularly in regard to *clostridium difficile* infection, rifamycin resistance in *Staphylococcus aureus* carriers, and the risk of non-approved utilisation for traveller's diarrhoea.
- The request for the sponsor to provide pharmacokinetic data for paediatric population groups.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xifaxan (Rifaximin) 550 mg tablet blister pack for oral administration, indicated for:

Prevention of the recurrence of hepatic encephalopathy where other treatments have failed or are contraindicated.

Specific conditions applying to these therapeutic goods

1. The Risk Management Plan (RMP) for rifaximin, version 1.2, dated 20 April 2012, to be revised as specified in sponsor's correspondence dated 1 May 2012 must be implemented, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

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

Therapeutic Goods Administration

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Reference/Publication #