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RESEARCH**

APPLICATION NUMBER:

21-361

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA	21-361
Drug Product, Brand[®]	Rifaximin, 
Submission Date	November 25, 2003
Applicant	Salix Pharmaceuticals Inc
Clinical Division	DSPIDP (HFD-590)
OCPB Division	DPE3 (HFD-880)
Type of Submission	NDA resubmission
Reviewer	Dakshina Chilukuri, Ph D
Team Leader	Philip Colangelo, Pharm D , Ph D
Review Date	May 07, 2004

I *Executive Summary*

The applicant is seeking approval of Rifaximin 200 mg in NDA 21-361 for the treatment of traveler's diarrhea. The applicant submitted a previous application for the same product and indication in 2001. Due to lack of conclusive evidence of efficacy of rifaximin in the treatment of traveler's diarrhea, the applicant was issued an approvable letter in 2002 requesting additional Phase III efficacy trial. The Clinical Pharmacology and Biopharmaceutics (CPB) review of the original NDA was performed by Kofi Kumi, Ph D, please refer to Dr. Kumi's review for additional CPB information of rifaximin (October 17, 2002). In addition to the efficacy study, three clinical pharmacology studies to characterize the PK of rifaximin in patients and drug interaction potential of rifaximin were requested.

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV. The rifamycins are a group of structurally similar complex macrocyclic antibiotics originally isolated from *S. mediterranei*. Rifaximin acts by binding to the beta-subunit of the bacterial DNA dependent RNA polymerase, resulting in inhibition of bacteria protein synthesis. Rifaximin is practically insoluble in water and poorly absorbed after oral administration, thus it is intended to be used locally to treat disease conditions where the desired site of action is the gastrointestinal tract.

In this resubmission, the applicant has submitted data from one efficacy trial, one clinical pharmacology study evaluating the PK of rifaximin in patients and two drug interaction studies with oral contraceptives and midazolam. The results of the clinical pharmacology studies indicated that rifaximin is poorly absorbed from the gastrointestinal tract, characterized by low systemic exposure. The PK of rifaximin in patients was found to be similar to healthy subjects. The drug interaction studies indicated that rifaximin does not alter the PK of oral contraceptives and oral and IV midazolam.

HFD-590 recommends approval of NDA 21-361 for Rifaximin 200 mg tablets based on the results of the efficacy studies.

A *Recommendations*

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the Clinical Pharmacology and Biopharmaceutics information included in the resubmission of NDA 21-361 for rifaximin and the reviewer has deemed this information to be acceptable. The Human Pharmacokinetics and

Bioavailability Section of NDA 21-361 has met the requirements of the 21 CFR 320 and the clinical pharmacology labeling requirements of 21 CFR 201.56

B Phase IV Commitments

There are no clinical pharmacology and biopharmaceutics Phase IV commitments

Comments (not to be sent to the applicant)

The presumed site of action of rifaximin to treat Traveler's Diarrhea is locally within the gastrointestinal tract (G I T). However, in the NDA, it appeared that no studies have been conducted to evaluate the potential effects of other co-administered drugs that alter gastrointestinal pH on rifaximin absorption and/or its effect locally within the G I T.

This comment was conveyed to the applicant. In response to the comment, the applicant provided a scientific justification for not conducting the above-mentioned studies. The justification is acceptable and is included in Appendix-D.

Labeling

The proposed label for rifaximin with clinical pharmacology/biopharmaceutics comments is provided in Appendix-A.

Dakshina Chilukuri, Ph D
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Pharm D, Ph D
cc NDA 21-361, HFD-590, HFD-880 and CDR (Biopharm)

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II Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics in patients

The PK of rifaximin was studied in 15 healthy male and female volunteers. Volunteers were challenged with a suspension of *Shigella flexneri* and administered rifaximin treatment (200 mg every 8 hours for 3 days) as soon as they met the case definition of diarrhea. Blood samples for analysis of plasma rifaximin pharmacokinetics were collected on Day 1 (pre-challenge), immediately before the 3rd, 5th, 7th and 9th rifaximin doses, and serially after the 3rd and 9th rifaximin doses. Rifaximin concentrations and exposures were low and highly variable on Day 1 and Day 3 in subjects challenged with *S flexneri*. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). The pharmacokinetic parameter estimates from this study were consistent with values previously observed for rifaximin in healthy volunteers.

Drug-Drug Interactions

Oral Contraceptives

28 subjects were enrolled in this study and they received a single dose (2 tablets) of the oral contraceptive, Ortho-Cyclen (0.50 mg of norgestimate and 0.07 mg of ethinyl estradiol), on Day 0 (Treatment A). Blood samples were collected at specified intervals after dosing to determine the plasma concentration-time profile of the OC components, ethinyl estradiol, and the two active metabolites of norgestimate, 17-deacetylnorgestimate, and norgestrel. Following a one-week washout period, subjects received rifaximin 200 mg administered orally every 8 hours for 3 days (9 consecutive oral doses) as follows: 2 doses on Study Day 11, 3 doses on Day 12 and Day 13, and one dose on Day 14. On Study Day 14 subjects received a single oral dose of Ortho-Cyclen concomitantly with a single dose of rifaximin (Treatment B). Blood samples were collected at specified intervals after dosing to determine the plasma concentration-time profile of the OC components (ethinyl estradiol, 17-deacetylnorgestimate, and norgestrel). In addition, for the first 8 hours after dosing, blood samples were collected for the determination of plasma rifaximin concentrations. The pharmacokinetic profiles of ethinyl estradiol, and the active metabolites of norgestimate, norgestrel and 17-deacetylnorgestimate, were unaltered following oral administration of rifaximin, 200 mg every 8 hours for 3 days (9 consecutive doses). Overall, rifaximin taken either alone or in combination with Ortho-Cyclen appeared to be well tolerated.

Midazolam

26 healthy subjects were enrolled in the study to determine the pharmacokinetics, safety and effect of rifaximin 200 mg administered orally every 8 hours for 3 days (9 consecutive PO doses) and 7 days (21 consecutive PO doses) on the disposition and hydroxylation of midazolam, a CYP3A probe, following a single dose of either midazolam 2 mg IV (given over 30 minutes) or midazolam 6 mg PO syrup in healthy subjects.

Pharmacokinetic analysis of midazolam, 1'-hydroxymidazolam and rifaximin plasma concentration-time profiles was performed. The pharmacokinetics of midazolam and its major metabolite, 1'-hydroxymidazolam, following IV and PO doses were unaltered with

concomitant PO administration of rifaximin, 200mg every 8 hours for 3 days (9 consecutive doses) or for 7 days (21 consecutive doses)

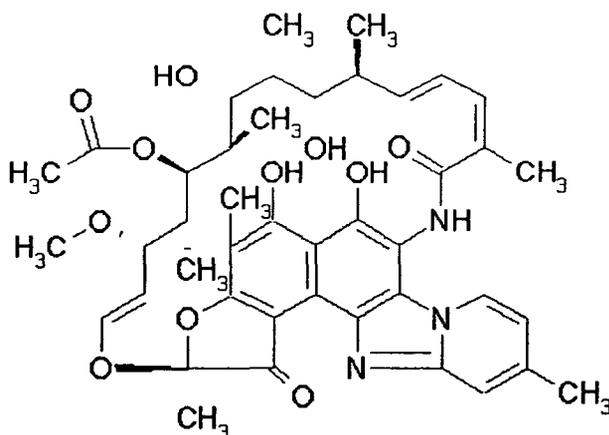
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ON ORIGINAL**

III Question Based Review

A General Attributes

- 1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Tablets contain rifaximin, a semi-synthetic, non-systemic antibiotic with antibacterial activity against enteric pathogens for gastrointestinal infections. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2- α]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9. The chemical structure is represented below.



Tablets for oral administration are film-coated and contain 200 mg of rifaximin. Inactive ingredients are sodium starch glycolate, glycerol palmitostearate, colloidal silicon dioxide, microcrystalline cellulose, talc, hydroxypropylmethylcellulose, titanium dioxide, disodium edetate, propylene glycol, and red iron oxide.

- 2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The efficacy of (rifaximin) Tablets in the treatment of travelers' diarrhea was evaluated in two pivotal trials. Study No. RFID3001 was conducted at clinical sites in Mexico, Guatemala, Peru, and India and compared the efficacy of

Tablets (200 mg orally 3 times daily [t i d]) for 3 days to placebo and ciprofloxacin (500 mg orally twice daily [b i d]) for 3 days The predominant pathogens in this trial were enterotoxigenic and enteroaggregative strains of *Escherichia coli* Approximately 20% of patients were culture-positive for prototypic inflammatory/invasive enteric pathogens such as *Campylobacter jejuni* and *Shigella* species The primary clinical endpoint in this trial was shortening the duration of diarrhea as defined by TLUS (Time to Last Unformed Stool) Stool specimens were cultured prior to treatment to isolate and identify infecting organisms and test their susceptibility Cultures were generally repeated the day after the treatment ended

The clinical response rates are displayed in Table 2 for the intent-to-treat population Improvement in TLUS in patients on Tablets was highly statistically significant versus placebo (p = 0 0014) The clinical performance of Tablets was enhanced by an analysis that excluded patients having fever ≥100 °F and/or blood in the stool and was comparable to that achieved with ciprofloxacin (see WARNINGS) TLUS results in the intent-to-treat population are displayed in Table 1 The overall microbiologic eradication rate for those patients with a pathogen identified at baseline and at least one post treatment stool sample was 50 0% for placebo, 60 2% for rifaximin, and 79 3% for ciprofloxacin

Table 1 Clinical Response Rates in Study No RFID3001				
	Tablets, 200 mg t i d	Placebo	Ciprofloxacin, 500 mg b i d ^a	Tablets vs Placebo
Intent-to-Treat Population				
	N = 197	N = 101	N = 101	
Clinical Response (Median TLUS)	32 0 h	65 5 h	28 8 h	p = 0 0014
95% CI	24 3–44 9	40 2–83 5	23 6–48 0	
Intent-to-Treat Population Excluding Patients With Fever and/or Blood in Stool				
	N = 116	N = 60	N = 65	
Clinical Response (Median TLUS)	23 3 h	48 1 h	27 4 h	p = 0 0002
95% CI	14 3–29 3	25 6–96 0	17 7–41 7	
^a = The approved use of ciprofloxacin for the treatment of infectious diarrhea is 500 mg b i d for 5–7 days				
CI = Confidence interval				

B General Clinical Pharmacology

- 1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to III F, Analytical Section, if no, describe the reasons)
Yes, please refer to III F, Analytical Section

2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

No formal exposure response analysis was conducted

a) are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

There are no unresolved dosing and administration issues

3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The plasma drug concentration measurements were found to be similar between healthy subjects and patients. Please see below for a comparison of the PK parameters between healthy subjects and patients

a) what are the basic PK parameters?

The mean (CV as %) PK parameters in healthy volunteers following single dose administration of 400 mg rifaximin (given as 2 × 200 mg) are given below (adapted from biopharmaceutics review dated 10/17/2002 by Kofi Kumi, Ph D)

Pharmacokinetic Parameter	(n = 14)
C_{max} (ng/L)	3.8 ± 1.3
AUC_{0-last} (ng·h/mL)	13.1 ± 7.6
CL_{0-24} (L/h)	7.14 ± 1.23
% Excreted	0.0509 ± 0.0172
$t_{1/2}$ (h)	5.84 ± 4.33
T_{max} (h)	1.21 ± 0.5

The PK parameters of rifaximin in patients were estimated using the noncompartmental approach, upon administration of 200 mg tablet of rifaximin TID for 3 days are given below

Mean PK Parameter (%CV)	Mean (%CV) Dose # 3	Mean (%CV) Dose # 9
C_{max} (ng/mL)	1.63 (53.02)	1.23 (42.76)
AUC_{0-last} (ng·h/mL)	6.95 (74.10)	7.83 (63.10)
T_{max} (hours)	2.77 (80.96)	2.11 (74.84)

b) does mass balance study suggest renal or hepatic as the major route of elimination? After oral administration of 400 mg ¹⁴C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine. Please see NDA review dated 10/17/2002 by Kofi Kumi, Ph D for additional details

4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The interindividual variability of the pharmacokinetic parameters in the three PK studies submitted as part of this NDA was high (45-60%)

C Intrinsic Factors

a) other factors that are important to understanding the drug's efficacy and safety
There are no other factors that need to be studied to understand the drug's efficacy and safety

D Extrinsic Factors

1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No systematic analysis of the effect of herbal products, diet, smoking, and alcohol use was conducted. The applicant conducted two drug-drug interaction studies to study the effect of oral and IV midazolam and oral contraceptives on coadministration with rifaximin. No effect of either substrate on the PK of rifaximin was found.

2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Rifaximin is poorly absorbed into the systemic circulation and the presumed site of action is the gastrointestinal tract. Hence, exposure response relationships are not expected to determine dosage regimens.

3 Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions?

Rifaximin was found to induce CYP3A4 enzyme at high concentrations. Please see NDA review dated 10/17/2002 by Kofi Kumi, Ph.D. for additional details.

b) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

There are no in vivo drug-interaction studies to indicate differences in exposure when the drugs were co-administered. The applicant performed 2 in vivo drug interaction studies with oral and IV midazolam and ortho-cyclen. The PK of midazolam and ortho-cyclen were not affected by rifaximin.

c) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There does not appear to be any mechanistic basis for drug-drug interactions. However, the applicant has not studied the influence of proton pump inhibitors (omeprazole) and antacids, which could potentially affect the local environment in the gastrointestinal tract and thus affect the absorption of rifaximin.

d) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

There are no unresolved issues related to metabolism, active metabolites and protein binding

E General Biopharmaceutics

1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Administration of high fat meal results in a 3 to 6-fold increase in the systemic exposure of rifaximin. Please see NDA review dated 10/17/2002 by Kofi Kumi, Ph D for additional details

2 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Following review of the original NDA submission in 2001, the applicant was advised to revise the dissolution method and the acceptance criteria. Based on the FDA reviewer's recommendation with the current submission, the applicant submitted a revised dissolution method and proposed the following conditions for the dissolution testing of rifaximin 200 mg tablets

Method Number	
Temperature	
Speed	
Volume	
Dissolution Medium	S
Sampling Volume	
Sampling Time	
Dissolution Specification	NLT - 80% at 2h

The proposed dissolution method and acceptance criteria are acceptable from a biopharmaceutics perspective

The applicant used the above method and performed dissolution testing on several batches of tablets. The results of those dissolution studies are given below

Table 4.2 60 Minute Dissolution Data for Rifaximin 200-mg Tablets Stability and Chemical Lots Using Method —

Packaged Batch No	F0758A002	F0758B002	F0758C002	F0982 001	C210193
Site of Manufacture	/				
Date of Manufacture	7/8/01	7/8/01	7/8/01	12/4/01	9/30/02
Bulk Tablet Batch No	F0758 002	F0758 002	F0758 002	F0982 001	C210193
Batch Purpose	Registration/ Stability	Registration/ Stability	Registration/ Stability	Clinical	Clinical
Packaging	/				
Storage Condition	25 °C/60% RH	25 °C/60% RH	25 °C/60% RH	Ambient	Ambient
Age of Sample					
Tablet #1					
Tablet #2					
Tablet #3					
Tablet #4					
Tablet #5					
Tablet #6					
Minimum					
Maximum					
% RSD	1.0	2.9	1.7	1.4	2.3
Average	87.6	90.3	81.8	77.1	79.4

As seen in the above table, the % RSD values are low (<3%) for various batches

The dissolution data for the 3 process validation batches (C2F0051, C2F0052 and C2F0053) and 2 clinical batches (F0982 001 and 99002) are given below

Table 3.1 Dissolution Profile for Rifaximin 200-mg Tablets Clinical Batches and Process Validation Batches

Rifaximin 200 mg Tablets Batch No	Percent Rifaximin Dissolved
C2F0051	
C2F0052	
C2F0053	
F0982 001	
99002	

14 Draft Labeling Page(s) Withheld

Appendix B Individual Study Reviews (available upon request)

Appendix C Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21 361	Brand Name	-	
OCPB Division (I, II, III)	III	Generic Name	Rifaximin	
Medical Division	DSPIDP	Drug Class	Antidiarrheal	
OCPB Reviewer	Dakshina M Chilukuri	Indication(s)	Traveler's diarrhea	
OCPB Team Leader	Philip Colangelo	Dosage Form	tablet	
		Dosing Regimen	200 mg 3 times a day for 3 days	
Date of Submission	11/26/03	Route of Administration	Oral	
Estimated Due Date of OCPB Review	04/24/04	Sponsor	Salix	
PDUFA Due Date	05/26/04	Priority Classification	Priority	
Division Due Date	05/01/04			
Clin. Pharm and Biopharm Information				
	X if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports tables data etc	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I Clinical Pharmacology				
Mass balance				
Isozyme characterization				
Blood/plasma ratio				
Plasma protein binding				
Pharmacokinetics (e.g. Phase I)				
<i>Healthy Volunteers</i>				
single dose				
multiple dose				
<i>Patients</i>				
single dose				
multiple dose	x	1		
Dose proportionality				
fasting / non fasting single dose				
fasting / non fasting multiple dose				
Drug drug interaction studies				
In vivo effects on primary drug	x	2		Drug Interaction study with oral and IV midazolam and oral contraceptives
In vivo effects of primary drug				
In vitro				
Subpopulation studies				
ethnicity				
gender				
pediatrics				
geriatrics				
renal impairment				
hepatic impairment				
PD				
Phase 2				
Phase 3				
PK/PD				

Phase 1 and/or 2 proof of concept				
Phase 3 clinical trial				
Population Analyses				
Data rich				
Data sparse				
II Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability				
solution as reference				
alternate formulation as reference				
Bioequivalence studies				
traditional design single / multi dose				
replicate design single / multi dose				
Food drug interaction studies				
Dissolution				
(IVIVC)				
Bio waiver request based on BCS				
BCS class				
III Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	X if yes	<u>Comments</u>		
<u>Application filable ?</u>	<u>X</u>			
<u>Comments sent to firm ?</u>		None		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC NDA 21 361 HFD 850(P Lee) HFD-880 (J Lazor), HFD-590(CSO) CDR

Response to the May 3, 2004 Clinical Pharmacology Inquiry

FDA's May 3, 2004 Email Inquiry

The presumed site of action of rifaximin to treat Traveler's Diarrhea is locally within the gastrointestinal tract (GIT). However, in the NDA, it appeared that no studies have been conducted to evaluate the potential effects of other co-administered drugs that alter gastrointestinal pH on rifaximin absorption and/or its effect locally within the GIT. Please provide the scientific justification and/or clarification for why these studies are not needed.

Salix Pharmaceuticals, Inc. Response

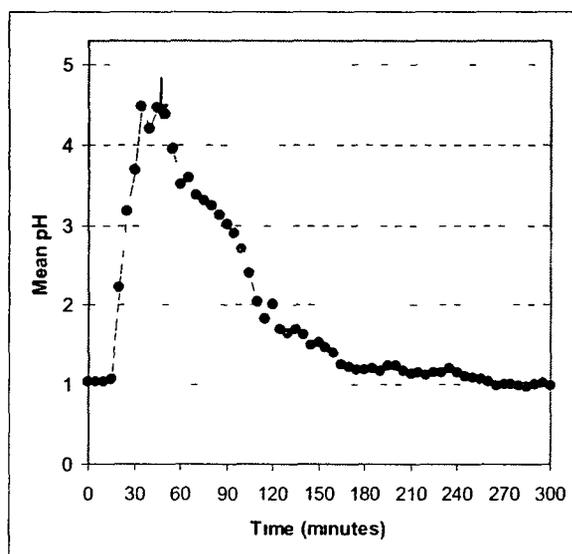
Salix has conducted a study of plasma and urinary pharmacokinetics of rifaximin after a single oral 400-mg dose during fasting and 30 minutes after a high-fat meal in 7 healthy subjects using a 2-way crossover design (N2270, original NDA Volume 028, page 001). The Table below summarizes the results.

Summary of Effect of a High Fat Meal on the Pharmacokinetic Measures of Rifaximin					
	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng hr/mL)	T _{1/2} (hr)	Urinary Excretion (% dose)
Fasting	3.8±1.3	1.2±0.5	18.3±9.5	6.0±1.9	0.0225±0.0085
High-Fat Meal	9.6±5.9	1.9±1.5	34.7±9.2	8.8±4.3	0.0509±0.0172

Data are means ± SD from 7 healthy subjects. Data are from Table 15 in Overall Summary of Application.

Although C_{max}, AUC and urinary excretion of rifaximin were higher with the high-fat meal than with fasting, total absorption of rifaximin as estimated by urinary excretion was less than 1% of the administered dose.

The Figure below illustrates the typical change in gastric pH following a standard meal



Results are means from 24 healthy subjects. The meal consisted of lean steak (125g), boiled potatoes (200-250g), fresh vegetables (200-250g), salad (50g), dessert (200mL) and water (200mL) over 30 min. Data are from Reference 1.

The figure illustrates that fasting gastric pH was approximately 1.0 and ingestion of the meal, which began at the time indicated by the vertical arrow, increased gastric pH to 4.5, after which it decreased to pH 1.0 over the subsequent 3 hours. A high-fat meal will produce a more sustained increase in gastric pH because of the fat-induced delay in gastric emptying.

Proton pump inhibitors generally produce little or no change in fasting gastric pH, in contrast to histamine H₂-receptor antagonists, which increase fasting gastric pH to above pH 3 (2, 3). Following a meal, the main effect of both proton pump inhibitors and histamine H₂-receptor antagonists is to prolong the increase in gastric pH induced by the meal (1, 4).

Since no important effect of a high-fat meal on the pharmacokinetics of rifaximin was observed, Salix has concluded that there is no important effect of gastric pH on rifaximin bioavailability. Therefore Salix does not believe it is necessary to not examine the effects of drugs that alter gastrointestinal pH on the pharmacokinetics of rifaximin or its effect locally within the gastrointestinal tract.

Additional information indicates that the pH of the gastrointestinal tract does not influence the absorption and/or the local effect of rifaximin within the gastrointestinal tract. The finding that over a pH range of 1 to 7 the solubility of rifaximin is ≤ 0.004 mg/mL (N4047, original NDA Volume 007, pages 149-241).

References

- 1 Gardner JD, Ciociola AA, Robinson M, McIsaac RL Determination of the time of onset of action of ranitidine and famotidine on intra-gastric acidity *Aliment Pharmacol Ther* 2002, 16 1317-1326
- 2 Hedenstrom H, Alm C, Kraft M, Grahnen A Intragastric pH after oral administration of single doses of ranitidine effervescent tablets, omeprazole capsules and famotidine fast-dissolving tablets to fasting healthy subjects *Aliment Pharmacol Ther* 1997, 11 1137-1141
- 3 Arnestad JS, Kleveland PM, Waldum HL In single doses ranitidine effervescent is more effective than lansoprazole in decreasing gastric acidity *Aliment Pharmacol Ther* 1997, 11 355-358
- 4 Bell NJV, Hunt RH Time to maximum effect of lansoprazole on gastric pH in normal male volunteers *Aliment Pharmacol Ther* 1996, 10 897-904

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Phil Colangelo
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BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA	21-361
Generic Name	Rifaximin
Brand Name	To be determined
Dosage Strength	200 mg Tablet
Proposed Indication	Treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by —
Dosage and Administration	Rifaximin can be administered orally with/or without food For — diarrhea, the recommended dose is one 200 mg tablet taken three times a day for 3 days
Applicant	Salix Pharmaceuticals, Inc
OND Clinical Division	DSPIDP (HFD-590)
OCPB Division	DPEIII (HFD-880)
Submission Type	3S
Submission Dates	12/26/01, 5/13/02, 7/2/02, 7/16/02, 7/19/02, 8/5/02
Review Date	10/17/02
Reviewer	Kofi A. Kumi, Ph D
Team Leader	Barbara Davit, Ph D

Executive Summary

Background Rifaximin is intended for the treatment of traveler's diarrhea. The proposed dosage regimen is one rifaximin tablet, 200 mg, to be taken orally, three times per day (tid), for 3 days.

Studies that characterize the pharmacokinetics of rifaximin when administered orally were submitted to the NDA. The studies were conducted in adult normal healthy subjects, patients with ulcerative colitis, Crohn's disease and hepatic encephalopathy. The two primary safety and efficacy studies submitted were randomized, comparative, controlled, phase 3 studies. One of the studies used a standard regimen of ciprofloxacin as an active control. The ciprofloxacin used in the study is not approved in the U.S. This study was determined to be inadequate and not reviewed by the medical reviewer. A bioequivalence study and dissolution information comparing the formulations of ciprofloxacin associated with this study were submitted but not reviewed. The sponsor did not submit a pharmacokinetic study that evaluated the exposure levels in patients with traveler's diarrhea. Rifaximin is practically insoluble in water and is poorly absorbed after oral administration, thus it is proposed to be used locally to treat disease conditions where the desired site of action is the gastrointestinal tract. Based on the inherent insolubility of rifaximin, the primary aim of the pharmacokinetic studies was to verify the extent of systemic absorption of the drug.

Rifaximin is concentrated in the gastrointestinal tract, the site of action, and is excreted primarily in feces as unchanged drug. The extent of systemic exposure to rifaximin after oral administration is not clear. However, less than 1% of an administered oral dose is excreted in the urine. In vitro hepatocyte studies, rifaximin induced cytochrome P450 3A4 (CYP3A4) at concentrations between 0.2 to 20 μ M. The greatest activity was 1.8 times control activity which was observed at

the 10 μ M concentration. The lowest concentration that caused CYP3A4 enzyme induction (0.2 μ M or 158 ng/mL) is about 50 times greater than peak plasma concentrations anticipated after dosing rifaximin at 200 mg tid. Rifaximin, at concentrations ranging from 2 to 200 ng/mL, showed no potential to inhibit cytochrome P450 enzymes. A high fat meal increases the extent of systemic absorption by approximately 3-fold. However, the exposure was still minimal and the clinical implications are not clear. The sponsor is recommending that Rifaximin be administered with or without food. The clinical studies were conducted with or without food and the sponsor reported no serious adverse events in the clinical studies and agreed to by the medical reviewer, therefore, the sponsor's recommendation is acceptable.

The primary safety and efficacy studies were randomized, comparative, controlled, phase 3 studies. One study was designed as a non-inferiority study and the other was designed as a superiority study. One study (RFID9701) compared the clinical efficacy and safety of 400 mg bid to a standard regimen of ciprofloxacin. The other study (RFID9801) was a placebo-controlled study that investigated the superiority of the clinical safety and efficacy of rifaximin at 200 mg tid and 400 mg tid. In the clinical studies, time to last unformed stool (TLUS) was predefined as the primary efficacy endpoint. A comparison of three different dose levels of rifaximin evaluated 200 mg tid, 400 mg bid or 400 mg tid was reported by the sponsor to show similar degrees of efficacy with TLUS values of 32.5 hours, 25.7 hours and 32.9 hours, respectively. Each of these values compares favorably with that observed for placebo-treated patients (TLUS 60.0 hours). Dose selection for these primary phase 3 safety and efficacy studies was based on the range of daily doses administered in a Phase 2 dose ranging study which showed a similar safety and efficacy profile for three doses of rifaximin (200 mg tid, 400 mg tid and 600 mg tid) to trimethoprim/sulfamethoxazole (TMP/SMX).

Recommendation The data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-361 to fulfill section 320 and 201.5 of 21CFR, Rifaximin 200 mg tablet is acceptable. It is highly recommended that the sponsor provide the follow additional data:

- 1) The extent of systemic exposure of rifaximin in patients with traveler's diarrhea should be evaluated.
- 2) The applicant Conduct an in vivo drug interaction study to evaluate whether there is an interaction between CYP 3A substrates and Rifaximin. The applicant could select one or two prototypical CYP 3A4 substrates that undergo significant presystemic metabolism likely to be co-administered with Rifaximin to study.
- 3) The applicant should provide individual and mean dissolution data comparing the lots used in the pivotal clinical safety and efficacy studies to the commercial lots using the proposed method and a f_2 calculation. The applicant should provide the similarity (f_2) calculations for such comparisons.
- 4) The applicant should provide the individual data for the dissolution information submitted to the agency with a letter date of 8/5/02. The submission contained dissolution comparing the clinical lot 99002 to commercial lots F0982 001, C2F0051, C2F0052 and C2F0053.

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Reviewer
Clin Pharm/Biopharmaceutics
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Concurrence

Barbara Davit, Ph D
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Summary of Clinical Pharmacology and Biopharmaceutics Findings

Four hundred milligrams (5x 80-mg capsules) of ¹⁴C- Rifaximin was administered to 4 healthy subjects. Blood, urine and feces samples were collected at specified time periods. Radioactivity was detected in plasma only during 0.5 to 4 hours after dosing with maximum mean plasma concentration of 20.6 ng-equivalents/mL at 1.5 hours. Almost all of the radioactivity was excreted in the feces as rifaximin. The proportion that was absorbed was extensively metabolized with only 0.03% of dose excreted as unchanged in the urine within 12 hours of dosing. Less than 1% of the dose was excreted in urine as rifaximin-associated radioactivity. In patients in whom rifaximin concentrations in bile were evaluated, rifaximin concentrations ranged from ~ μg/mL. Within 7 days of dosing, nearly 100% of the radioactivity associated with the rifaximin dose was recovered.

The following table provides the excretion in urine and feces after oral administration of ¹⁴C-Rifaximin (400 mg) to male human subjects

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Table 1

**Excretion of radioactivity in urine and faeces after oral administration of
¹⁴C-rifaximin (400 mg) to male human subjects**

Results are expressed as total % dose

Time (hours)	Subject number and sex				Mean ± sd M
	1M	2M*	3M	4M	
Urine					
0 - 2					0.07 ± 0.07
2 - 4					0.10 ± 0.02
4 - 6					0.07 ± 0.04
6 - 8					0.02 ± 0.01
8 - 10					0.03 ± 0.03
10 - 12	nd				0.01 ± 0.01
12 - 24	nd	nd			0.02 ± 0.02
24 - 48	nd	nd	nd		-
48 - 72	nd	nd	nd	nd	-
72 - 96	nd	nd	nd	nd	-
96 - 120	nd	nd	nd	nd	-
120 - 144	nd	nd	nd	nd	-
144 - 168	nd	nd	nd	nd	-
Total in urine					0.32 ± 0.05
Faeces					
0 - 24	-	nd	-	ns	18.37 ± 16.33
24 - 48	/	/	/	/	28.64 ± 27.38
48 - 72	/	/	/	/	45.88 ± 38.92
72 - 96	/	/	/	ns	0.47 ± 0.40
96 - 120	/	nd	nd		3.14 ± 5.42
120 - 144	/	nd	nd	-	0.09 ± 0.08
144 - 168	nd	-	nd	-	-
Total in faeces					96.62 ± 5.67
Total recovery					96.94 ± 5.64

* Not included in mean calculations

sd Standard deviation

ns No sample (where used in mean calculation, this is included as zero)

nd No radioactivity detected (where used in the mean calculation, this is included as zero)

Pharmacokinetic data were obtained from healthy subjects, patients with ulcerative colitis, Crohn's disease and hepatic encephalopathy. Pharmacokinetic studies in both healthy subjects and patients following single and multiple oral doses demonstrate that less than 1% administered dose is excreted in urine. While only trace amounts of parent drug and metabolites are detected in the urine, there is high fecal recovery of rifaximin primarily as unchanged drug. Upon repeated administration, there is little or no drug accumulation. Food increases the extent of absorption by approximately 3-fold when compared to administration under fasting conditions.

In a multiple dose study, patients with cirrhosis and mild to moderate encephalopathy were treated with rifaximin 600, 1200 and 2400 mg/day in three divided doses for 7 days. The following table contains the mean plasma and urine concentration after administration of the proposed dosing regimen of 200 mg tid.

Table 2 Mean Concentrations of Rifaximin in Plasma on Day 1 and in Urine On Day 7 from a 7-Day Multiple Dose Study of 200 mg Three Times Daily

Parameter	Plasma Concentration (ng/mL)	Urine Concentration (ng/mL)	Urine Volume (mL)	Total Amount (mg)	% dose excreted unchanged
Mean	2.69	518.3	1308	0.367	0.061
SD	3.95	854.0	603	0.393	0.066
%CV	1.47	165	46	107	107
Min					
Max					
N	16	13	13	13	13

The percentage of the dose of rifaximin excreted unchanged in the urine was minimal.

The potential of rifaximin for inhibition of cytochrome P450 isozymes was evaluated in vitro with human liver microsomes. Rifaximin at concentrations ranging from 2 to 200 ng/mL showed no potential to inhibit human hepatic microsomal cytochrome P450 isozymes that included CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

The comparative induction potential of rifaximin was evaluated against rifampin, a known inducer of hepatic CYP3A4/5, in an in vitro assay with human hepatocyte cultures. Human hepatocyte cultures were incubated with rifaximin or rifampin at concentrations of 0.2, 1, 10, 20, and 50 mM (or approximately 0.16, 0.8, 8, 16, and 40 mg/mL, respectively). Following incubation for 3 days, the rate of testosterone 6- α -hydroxylation was determined in microsomes. Rifaximin at a concentration of 10 mM showed up to a 1.8-fold increase in CYP3A4/5 activity when compared to controls. Rifampin at all concentrations evaluated, i.e., 0.2 to 50 mM showed a 3 to 4-fold increase in activity in comparison to controls.

The highest concentration of rifaximin used in the induction studies, 50 μ M (39 μ g/mL), was toxic to the hepatocytes. The clinical relevance of this observation is not known. The concentration at which toxicity was observed is about 3 orders of magnitude greater than plasma concentrations anticipated at the 200-mg tid regimen.

Dissolution The dissolution method selected by the sponsor for the release and stability testing of the drug product is provided below:

Apparatus _____
 Media _____
 Volume _____
 Temperature _____
 Speed _____
 Sampling time _____
 Proposed dissolution specification Q = _____ at _____

The media was selected because /

This reviewer disagrees with the selection of a / . It is recommended that a / be used. Based on the dissolution data provided, the following interim specification is recommended $Q = -$ at $-$. Hence, the following interim method and specification is recommended

Apparatus
Media

Volume
Temperature
Speed

Specification

The sponsor should provide dissolution information from the clinical study and commercial lots using the method with a / to enable setting a final specification

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What are the physicochemical attributes of Rifaximin?

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV. The rifamycins are a group of structurally similar complex macrocyclic antibiotics originally isolated from *S. mediterranei*. Rifaximin acts by binding to the beta-subunit of the bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial protein synthesis. Rifaximin is practically insoluble in water and was poorly absorbed after oral administration, thus it is intended to be used locally to treat disease conditions where the desired site of action is the gastrointestinal tract. Based on the inherent insolubility of rifaximin, the primary aim of the pharmacokinetic studies was to verify the systemic absorption of the drug.

The following tables contain the proposed formulation for the rifaximin tablet.

Table 3a Rifaximin Core Tablet Composition

Component	Mg/tablet
Rifaximin	200
Sodium Starch glycolate (NF)	/
Glycerol palmitostearate (FCC)	
Colloidal silicon dioxide (NF/Ph Eur)	
Microcrystalline cellulose (NF/Ph Eur)	
Talc (USP/Ph Eur)	
Total Weight of Core Tablet	

Table 3b Rifaximin Coating Composition

Component	Mg/tablet
/	

What is the extent of systemic exposure after administration of Rifaximin orally?

The extent of systemic absorption of rifaximin after oral administration is not clear from the studies submitted. However, less than 1% of an administered dose is detected in the urine as unchanged drug and the majority of rifaximin is detected in the feces.

The sponsor submitted single and multiple dose studies that measured concentrations of rifaximin in plasma and urine. In a single dose study in which 18 male volunteers were administered rifaximin 400 mg (2 x 200 mg tablets) after an overnight fast, rifaximin was below limit of detection of the assay in most patients. In some patients, very low amounts were detected at different times. Low amounts of rifaximin were detected in urine, less than 0.01% of the administered dose is found in the urine by the 48th hour. The following table provides the results from the study.

Table 4 Plasma Concentrations of Rifaximin (ng/mL) in Healthy Volunteers

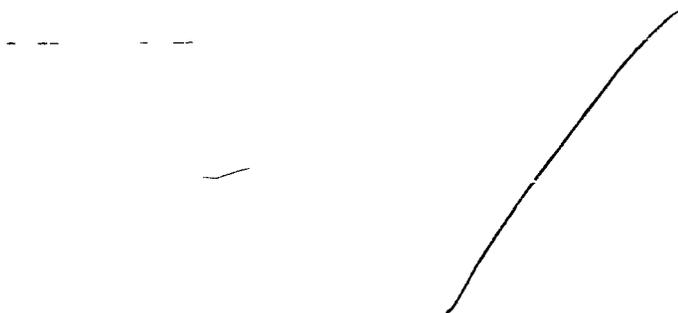
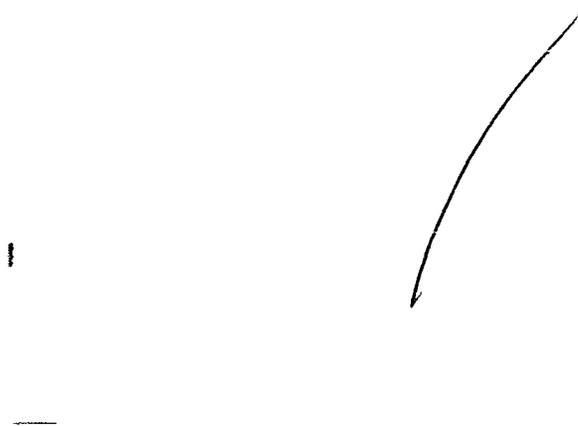


Table 5 Urinary Concentrations of Rifaximin During the Urine Collection Intervals



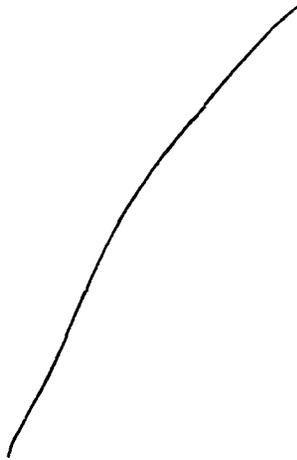


Table 5 contd (above)

Plasma and urine concentration were determined in patients with ulcerative colitis who received single 400 mg dose of rifaximin after an overnight fast. Minimal concentrations were detected sporadically at different time points but most measurements were below the detection limit of —. Less than 0.025% of the administered dose was found in the urine by the 24-hour time point. Similarly, minimal plasma and urine concentrations were obtained from patients with Chron's disease who were administered a single 400 mg dose of rifaximin. The results are similar to that observed for healthy patients administered rifaximin. The following tables provide plasma and urine concentrations of rifaximin after administration of 400 mg to patients with Chron's disease. The analytical method was LC/MS/MS with a limit of detection of — and a linear range of —.

PT no	Time (hours)				
	0	1	4	8	24
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
Mean	0 0	2 74	1 59	2 11	1 61
SD	0 0	3 18	1 40	3 28	2.60

Table 6 (above) Plasma concentrations (ng/mL) of rifaximin detected in each patient

Table 7 Rifaximin urinary excretion over 0 – 48 hour time intervals and percentage of the administered amount excreted by each patient

Pt no	0-24hrs		0-48 hrs	
	Total Amt (ng)	% of the Drug Excreted	Total Amt (ng)	% of the Drug Excreted
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
Mean	28877	0 0072	43106	0 0108
SD	19126	0 0048	25431	0 0064

In a multiple dose study, patients with cirrhosis and mild to moderate encephalopathy were treated with rifaximin 600, 1200 and 2400 mg/day in three divided doses for 7 days. Very limited plasma concentrations were detected at each dose level studied. The increase in plasma concentration was not proportional to dose. The lower limit of quantitation of the LC/MS-MS assay was $\mu\text{g/mL}$. The following tables contain the plasma and urine concentrations at each of the dose levels studied. Plasma samples were obtained approximately 3 hours after the first drug dose on day 1.

Table 8 Concentrations of Rifaximin in Plasma on Day 1 and in Urine on Day 7 from a 7-Day Multiple Dose Study of 200 mg Three Times Daily (600 mg/day)

Subject	Plasma Conc. (ng/mL)	Urine Conc. (ng/mL)	Urine Volume (mL)	Total Amount (mg)	% dose excreted unchanged
3					
5					
9					
10					
13					
18					
28					
33					
35					
37					
41					
45					
46					
56					
59					
63					
66					
69					
Mean	2.69	518.3	1308	0.367	0.061
S.D.	3.95	854.0	603	0.393	0.066
%CV	147	165	46	107	107
Min					
Max					
N	16	13	13	13	13

LLOQ = Lower Limit of Quantitation
 NS = No Sample
 NC = Not Computed

Table 9 Concentrations of Rifaximin in Plasma on Day 1 and in Urine on Day 7 from a 7-Day Multiple Dose Study of 400 mg Three Times Daily (1200 mg/day)

Subject	Plasma Conc. (ng/mL)	Urine Conc (ng/mL)	Urine Volume (mL)	Total Amount (mg)	% dose excreted unchanged
1					
4					
7					
11					
15					
17					
30					
32					
36					
38					
42					
43					
47					
49					
55					
58					
61					
65					
67					
Mean	10.50	966.9	1653	1.199	0.100
S D	15.53	895.6	1193	1.119	0.093
%CV	148	93	72	93	93
Min					
Max					
N	13	15	15	15	15

LLOQ = Lower Limit of Quantitation

NS = No Sample

NC = Not Computed

Subject	Plasma Conc. (ng/mL)	Urine Conc. (ng/mL)	Urine Volume (mL)	Total Amount (mg)	% dose excreted unchanged
2					
6					
8					
12					
14					
16					
29					
31					
34					
39					
40					
44					
57					
60					
62					
64					
68					
Mean	13.47	1102.4	1231	1.350	0.056
S.D.	14.84	1167.4	495	1.899	0.079
%CV	110	106	40	141	141
Min					
Max					
N	14	15	15	15	15

LLOQ = Lower Limit of Quantitation

NS = No Sample

NC = Not Computed

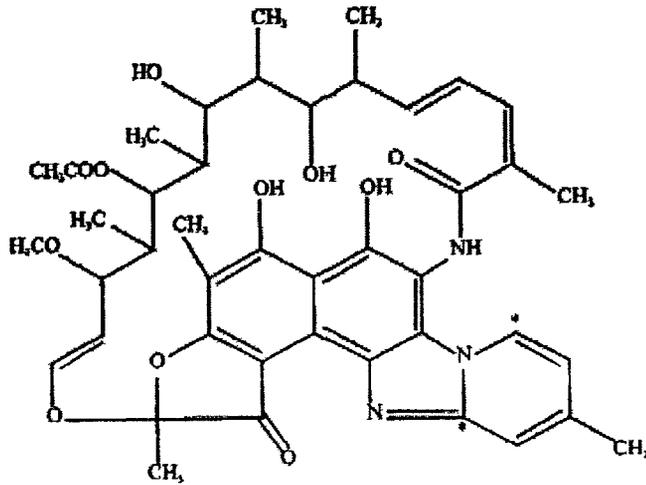
Table 10 (above) Concentration of Rifaximin in Plasma on Day 1 and in Urine on Day 7 from a 7-Day Multiple Dose Study of 800 mg Three times Daily (2400 mg/day)

What is the Metabolism and Disposition of Rifaximin after Oral Administration?

Following oral administration of 400 mg of ¹⁴C- Rifaximin, the majority of rifaximin was excreted in the feces. Plasma concentrations were minimal and the small amount absorbed was extensively metabolized. A small fraction (0.03% of administered dose) was excreted in the urine unchanged. Fecal excretion appears to be the primary mode of elimination of rifaximin with most excreted unchanged.

Four hundred (5x 80-mg) milligrams of ¹⁴C- Rifaximin was administered to 4 healthy subjects. The batch of ¹⁴C- Rifaximin had a specific activity of 0.126 μCi/mg and radiochemical purity

— The following figure indicates the position of the radiolabeled carbon



Structure of ¹⁴C-rifaximin * Denotes the positions of radiolabelling

Fig 1

Radioactivity was measured with automatic liquid scintillation analyzers. Profiling of urine and extracts of plasma and feces was carried out by high performance liquid chromatography. Following oral administration of 400 mg of ¹⁴C-Rifaximin, small concentrations of rifaximin were measured in plasma during 0.5 to 24 hours. Radioactivity was detected in plasma only during 0.5 to 4 hours after dosing with maximum mean plasma concentration of 20.6 ng-equivalents/mL at 1.5 hours. Almost all of the radioactivity was excreted in the feces and were present as rifaximin. The small proportion that was absorbed was extensively metabolized with only 0.03% of dose excreted as unchanged drug in the urine within 12 hours of dosing. The following table contains the amount of rifaximin detected in plasma, urine and feces.

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**Concentrations of radioactivity in plasma after oral administration of
¹⁴C-rifaximin (400 mg) to male human subjects**

Concentrations are expressed as ng equivalents/ml plasma

Time (hours after dosing)	Subject number				Mean ± sd
	1	2	3	4	
0.25	nd	nd	nd	nd	-
0.5		nd		nd	-
0.75			nd	nd	-
1				nd	171 ± 159
1.5				nd	206 ± 147
2				nd	191 ± 137
3				nd	130 ± 89
4	nd	nd			-
6	nd	nd	nd	nd	-
8	nd	nd	nd	nd	-
10	nd	nd	nd	nd	-
12	nd	nd	nd	nd	-
16	nd	nd	nd	nd	-
24	nd	nd	nd	nd	-
36	nd	nd	nd	nd	-
48	nd	nd	nd	nd	-
72	nd	nd	nd	nd	-
96	nd	nd	nd	nd	-
120	nd	nd	nd	nd	-
144	nd	nd	nd	nd	-
168	nd	nd	nd	nd	-

sd Standard deviation

nd Not detected (< about 10 ng equivalents/ml plasma) Where used in mean calculations, such values were included as zero

Table 11 (above)

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Table 12

Concentrations of rifaximin in plasma after oral administration of ¹⁴C-rifaximin (400 mg) to male human subjects

Concentrations are expressed as ng rifaximin/ml plasma

Time (hours after dosing)	Subject number				Mean ± sd
	1	2	3	4	
0.25	BLQ	BLQ	BLQ	BLQ	-
0.5			BLQ	BLQ	-
0.75				BLQ	16 ± 1.5
1				BLQ	2.2 ± 1.5
1.5					19 ± 0.9
2					25 ± 1.1
3					21 ± 1.5
4		BLQ			27 ± 3.9
6		BLQ			12 ± 1.0
8	BLQ	BLQ			-
10	BLQ	BLQ			-
12	BLQ	BLQ			-
16	BLQ	BLQ			-
24	BLQ	BLQ			-
36	BLQ	BLQ	BLQ	BLQ	-
48	BLQ	BLQ	BLQ	BLQ	-
72	BLQ	BLQ	BLQ	BLQ	-
96	BLQ	BLQ	BLQ	BLQ	-
120	BLQ	BLQ	BLQ	BLQ	-
144	BLQ	BLQ	BLQ	BLQ	-
168	BLQ	BLQ	BLQ	BLQ	-

sd Standard deviation
 BLQ Below limit of quantification

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Table 13

Proportions of administered radioactivity accounted for by rifaximin excreted unchanged in urine

Results are expressed as % dose

Time (hours)	Subject number and sex				Mean \pm sd*
	1M	2M	3M	4M	
0-2					0.004 \pm 0.003
2-4					0.008 \pm 0.004
4-6					0.008 \pm 0.007
6-8					0.003 \pm 0.002
8-10					0.005 \pm 0.005
10-12					0.003 \pm 0.002
Total					0.030 \pm 0.020

ns No sample
 sd Standard deviation
 * Excluding Subject 2

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Excretion of radioactivity in urine and faeces after oral administration of ¹⁴C-rifaximin (400 mg) to male human subjects

Results are expressed as total % dose

Time (hours)	Subject number and sex				
	1M	2M*	3M	4M	Mean ± sd M
Urine					
0 - 2					0.07 ± 0.07
2 - 4					0.10 ± 0.02
4 - 6					0.07 ± 0.04
6 - 8					0.02 ± 0.01
8 - 10					0.03 ± 0.03
10 - 12					0.01 ± 0.01
12 - 24					0.02 ± 0.02
24 - 48					-
48 - 72					-
72 - 96					-
96 - 120					-
120 - 144					-
144 - 168					-
Total in urine					0.32 ± 0.05
Faeces					
0 - 24					18.37 ± 16.33
24 - 48					28.64 ± 27.38
48 - 72					45.88 ± 38.92
72 - 96					0.47 ± 0.40
96 - 120					3.14 ± 5.42
120 - 144					0.09 ± 0.08
144 - 168					-
Total in faeces					96.62 ± 5.67
Total recovery					96.94 ± 5.64

* Not included in mean calculations

sd Standard deviation

ns No sample (where used in mean calculation this is included as zero)

nd No radioactivity detected (where used in the mean calculation, this is included as zero)

Table 14 (above)

Table 15 Pharmacokinetic Parameters Calculated for Plasma Rifaximin

For rifaximin

Parameter	Subject number				Mean ± sd
	1	2	3	4	
Dose (mg)	396.6	396.5	396.5	396.8	396.60 ± 0.14
Bodyweight (kg)	72.2	71.6	62.2	76.2	70.55 ± 5.93
Dose (mg/kg)	5.49	5.54	6.37	5.21	5.65 ± 0.50
C _{max} (ng/ml) ^a					4.281 ± 2.846
T _{max} (hours)					
AUC _t (ng.hours/ml)					19.5 ± 16.5
AUC ₁₆₈ (ng.hours/ml)					21.7 ± 17.8
t _{1/2} (hours) ^e		-	-		-
k _{el} (hours ⁻¹) ^e		-	-		-
Ratio C _{max} (%) ^d	8.8	11.8	7.9	31.7	15.1 ± 11.2
Ratio AUC _t (%) ^d	16.5	10.3	26.6	-	17.8 ± 8.2
Ratio AUC ₁₆₈ (%) ^d	16.2	9.1	24.4	-	16.6 ± 7.7

sd Standard deviation

^aMaximum measure plasma concentration

^eTerminal rate constant and half life could not be adequately estimated

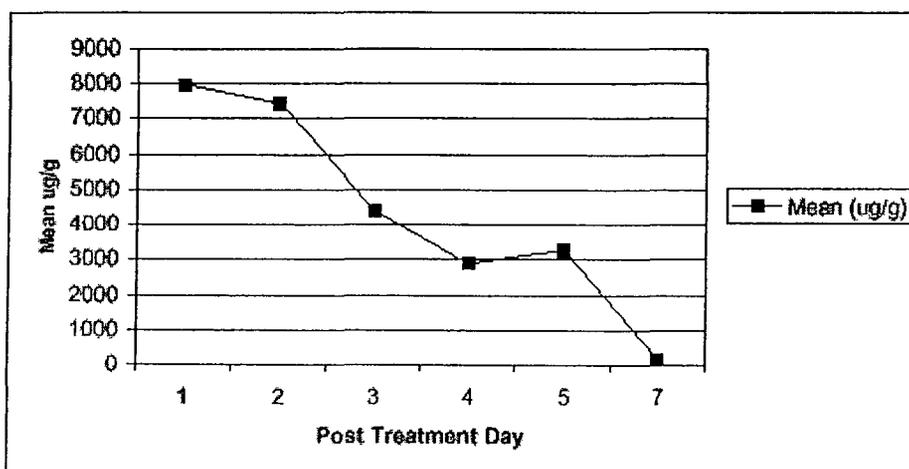
^dRatio (%) of the concentrations radioactivity

In a phase III safety and efficacy study in patients with travelers diarrhea who were administered rifaximin 400 mg twice a day for 3 days, fecal samples were collected in a subset of 38 patients for 7 days post treatment. Patients in the study received rifaximin 400 mg bid for 3 days. Following its administration, rifaximin was excreted as unchanged drug in feces. Plasma concentrations were not evaluated in this study. The following graph and table provide the amount of rifaximin in the feces at each time period post treatment that was evaluated.

Table 16

Post-Treatment Mean Stool Concentration (µg/g) ± SE (N = 38)					
Day 1	Day 2	Day 3	Day 4	Day 5	Day 7
7962 ± 4151	7425 ± 2563	4405 ± 1691	2892 ± 1409	3266 ± 3194	155 ± 71

Figure 2



The total amount of rifaximin excreted in the feces could not be evaluated, therefore, the percentage of dose excreted in the feces in this study is not known. However, the concentration of unchanged rifaximin determined per gram of stool was higher than that found in either plasma, bile, urine or feces in other studies. The results indicate rifaximin is detected in feces for at least 7 days after the last dose has been administered.

What is the Effect of Food on the Systemic Exposure of Rifaximin?

Food increases the plasma concentration of rifaximin detected after oral administration of a single dose 400 mg. Rifaximin taken after fasting or following a standardized high-fat breakfast resulted in C_{max}, T_{max} and AUC increasing by 286 ± 183%, 157 ± 85.4% and 273 ± 212%, respectively for a high fat breakfast compared with fasting. There was urinary recovery of rifaximin, but not following a high-fat breakfast compared with fasting.

In an open-label, randomized, crossover, phase 1 study, healthy adult volunteers were administered 400 mg rifaximin under fasting conditions or after a high fat meal (total calorie range 900 – 1000). The concentration of rifaximin and pH was determined using a high-pressure liquid chromatography mass-spectrometer (HPLC-MS) method. The lower limit of quantitation was 10 ng/mL in plasma and 10 ng/mL in urine. The following graph and tables provide the plasma concentrations and pharmacokinetic parameters for rifaximin.

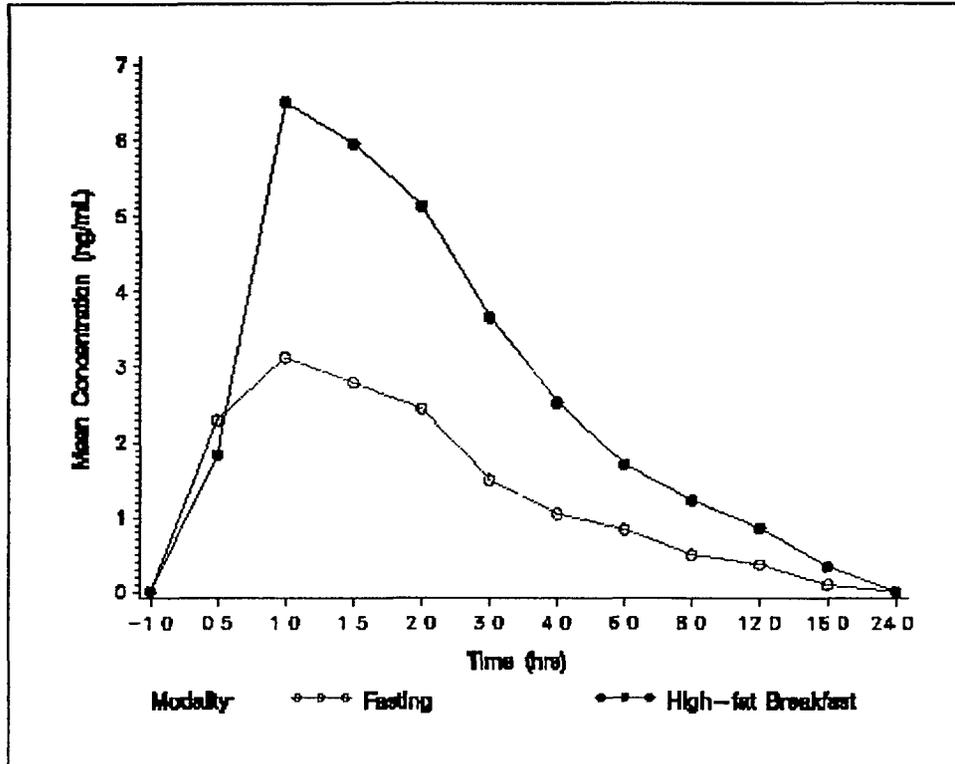


Fig 3 (above)

Table 17

Computed Pharmacokinetics Parameters for Rifaximin, (n=14)			
	High-Fat Breakfast (B)	Fasting (A)	
Parameter	Mean ± SD	Mean ± SD	p-Value ^a
C _{max} (ng/mL)	9.6 ± 5.9	3.8 ± 1.3	0.003
T _{max} (hours)	1.9 ± 1.5	1.2 ± 0.5	0.082
AUC _{last} (ng-hr/mL)	28.9 ± 9.3	13.1 ± 7.6	<0.001
AUC (ng-hr/mL)	34.7 ± 9.2	18.3 ± 9.5	<0.001
Half-life (t _{1/2}) in hours	5.95 ± 1.88	5.84 ± 4.33	0.309
%Excreted	0.0225 ± 0.0085	0.0509 ± 0.0172	<0.001
Cl _r 0-24 (L/hr)	8.78 ± 4.59	7.14 ± 1.23	0.170

Table 18

Ratios (Non-Fasting/Fasting) of Pharmacokinetics Parameters for Rifaximin, All Subjects (Log Transformed Scale)			
	Ratio	90% Compliance Interval	95% Compliance Interval
Parameter	(B/A) ^a	Lower Limit - Upper Limit	Lower Limit - Upper Limit
AUC _{last}	257.0%	175.1% - 377.2%	160.8% - 410.9%
AUC	215.9%	153.3% - 303.9%	142.1% - 328.0%
C _{max}	217.6%	143.2% - 330.6%	130.5% - 362.9%

^aA = 400 mg rifaximin PO, fasting, B= 400 mg rifaximin PO, high-fat breakfast

The mean peak plasma concentration of rifaximin (C_{max}) following a high-fat breakfast was significantly higher compared with after fasting. The mean total AUC increased to 34.7 ± 9.2 from 18.3 ± 9.5 ng-hr/mL after a high-fat breakfast. Although there was no significant difference (p = 0.082) between the two treatments (meal modalities) in the mean T_{max}, there was a trend toward a delayed T_{max} following a high fat breakfast (1.9 ± 1.5 versus 1.2 ± 0.5 hours). While the percentage of rifaximin excreted in the urine was minimal, administration of rifaximin with food increased the urinary recovery from 0.0225% to 0.0509% but had no influence on the urinary recovery of —. The sponsor is recommending that Rifaximin be administered with or without food. The clinical studies were conducted with or without food and the study that was determined acceptable with no serious adverse events, the applicant's recommendation is acceptable.

The sponsor reported that a dose of 400 mg rifaximin after either a fasting or high fat breakfast was well tolerated by healthy volunteer subjects. Adverse events reported were mild and resolved without sequelae per the sponsor. The majority of adverse events were of gastrointestinal origin.

Is Rifaximin detected in bile after oral administration?

Biliary excretion of rifaximin was minimal in patients with intact GI mucosa who were administered oral rifaximin prior to cholecystectomy.

Thirteen patients ranging from 30-81 years (mean age = 58 years) were studied. Cholecystectomy was performed for cholelithiasis in 11 patients and for adenoma of the gallbladder in the other two. None of the patients had an intestinal disease that could affect the absorptive function of the mucosa. Patients received rifaximin at 400 mg bid for 2 days (1600 mg total dose). The last dose was given 2 to 4 hours prior to surgery. Bile samples were taken from the gallbladder after excision. In all patients, oral cholecystography before surgery demonstrated a functioning gallbladder.

The following table contains the concentration of bile detected in each patient

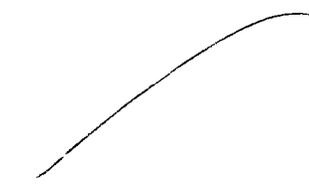
Patient No	Disease	Bile vol (mL)	Rifaximin conc (µg/mL)
1	gallbladder adenoma		
2	cholelithiasis		
3	cholelithiasis		
4	cholelithiasis		
5	cholelithiasis		
6	cholelithiasis		
7	cholelithiasis		
8	cholelithiasis		
9	cholelithiasis		
10	cholelithiasis, adenoma		
11	cholelithiasis		
12	cholelithiasis		
13	cholelithiasis		

The data indicate that concentrations in bile is low relative to that found in feces and support findings from other in vivo pharmacokinetic studies suggesting that absorption of rifaximin may be low following an oral dose

Does Rifaximin induce or inhibit cytochrome P450 enzyme system?

Rifaximin induced 3A4 in vitro at concentrations ranging from 0.2 to 50 μM . The lowest concentration studied (0.2 μM , or 158 ng/mL) is 50-100 times greater than peak exposures anticipated at 200 mg tid. It is not known if rifaximin would induce hepatic CYP3A4 at the proposed therapeutic regimen of 200 mg tid. Since rifaximin levels are high in the lumen of the small intestine during therapy, it is possible that repeated exposure to high intraluminal levels over the 3-day regimen may induce intestinal 3A4. Rifaximin, at concentrations ranging from 0.2 to 200 ng/mL, showed no potential to inhibit cytochrome P450 enzymes 1A2, 2A6, 3B6, 2C9, 2C19, 2D6, 2E1, and 2A4. IC_{50} values exceeded 200 ng/mL.

Human hepatocytes for induction experiments were grown by



Following the adaptation period, viable hepatocytes were treated daily with vehicle, test articles and positive control. The treatment period was for 3 days. Both rifaximin and rifampin were tested at concentrations of 0.2, 1.0, 10, 20, and 50 μM in MCM. Microsomal samples were prepared from the hepatocytes. To test for enzyme induction, the microsomal pellets from the treated hepatocyte cultures were assayed for protein content and for 6 β -hydroxylase (CYP3A4) activity.

The following table contains the effects of rifaximin and rifampin on the rate of testosterone 6 β -hydroxylation

Table 20

The effects of rifaximin and rifampin on rate of testosterone 6 β -hydroxylation				
Units are pmol/mg protein/minute				
Treatment	Concentration	Individual values	Mean	Fold induction
DMSO	0.1% (v/v)		3050	N/A
Rifampin (positive control)	0.2 μ M		9250	3.0
	1.0 μ M		11450	3.7
	10 μ M		12230	4.0
	20 μ M		9100	3.0
	50 μ M		9830	3.2
Rifaximin	0.2 μ M		4470	1.5
	1.0 μ M		5230	1.7
	10 μ M		5530	1.8
	20 μ M		4000	1.3
	50 μ M		468	0.15

Treatment of hepatocytes with rifaximin at concentrations of 0.2, 1.0, 10, and 20 μ M increased testosterone 6 β -hydroxylase activity. The greatest increase was at 10 μ M (1.8 times control activity). Treatment with 50 μ M rifaximin suppressed CYP3A4 activity, to 15% of control activity. Rifampin at all concentrations increased 6 β -hydroxylase activity up to 4 times control activity. In general, at the concentrations studied, rifaximin was less than 50% as effective as rifampin as an inducer of CYP3A4. The highest concentration of rifaximin (50 μ M) appeared to alter the morphology of the hepatocytes as observed by light microscopy. However, there were no clear signs of toxicity.

To study the inhibition potential of rifaximin, separate microsomal incubations were performed with probe substrates. All incubation mixtures contained microsomes, 0.1 M phosphate buffer pH 7.4 containing EDTA and MgCl₂, and a glucose-6-phosphate dehydrogenase-based NADPH generating system. Microsomal incubation times ranged from 15 to 30 minutes at 37°C. Rifaximin was added to incubation mixtures at concentrations of 0, 2, 6, 20, 60, and 200 ng/mL.

Rifaximin, at concentrations ranging from 2 to 200 ng/mL, showed no potential to inhibit cytochrome P450 enzymes 1A2, 2A6, 3B6, 2C9, 2C19, 2D6, 2E1, and 2A4. IC₅₀ values exceeded 200 ng/mL. For most enzymes tested, the % of activity remaining following incubation with rifaximin ranged from about 88 to 100%. However, the mean % of enzyme activity remaining for CYP2B6 ranged from 73.9 to 87.4% following incubation with rifaximin. There was no dose-response relationship between rifaximin and CYP2B6 activity, and the rifaximin IC₅₀ for CYP2B6 still exceeded 200 ng/mL.

Table 21

Activity Assay	P450 Enzyme	IC ₅₀ for Rifaximin (ng/mL)
7-Ethoxyresorufin Deethylase	CYP1A2	>200
Coumarin 7-Hydroxylase	CYP2A6	>200
7-Ethoxy-Trifluoromethyl Coumarin O-Deethylase	CYP2B6	>200
Tolbutamide 4-Methyl Hydroxylase	CYP2C9	>200
S-Mephenytoin 4'-Hydroxylase	CYP2C19	>200
Dextromethorphan O-Demethylase	CYP2D6	>200
p-Nitrophenol Hydroxylase	CYP2E1	>200
Erythromycin N-Demethylase	CYP3A4	>200

What analytical methods were used determining rifaximin concentrations?

Quantitation of rifaximin and its metabolites in plasma, urine and feces were analyzed by several high performance liquid chromatographic methods using radiometric, ultraviolet (UV) detection, electrochemical (EC) or mass spectrometric (MS/MS) detection. The analytical methodology is acceptable.

A liquid chromatographic mass spectrometric (LC-MS/MS) method was developed and validated for measurement of rifaximin in human urine and plasma over the concentration range of 0.5 to 40 ng/mL. The limit of quantitation was 0.5 ng/mL. The intra-day (within batch) precision assessed by the coefficients of variation of the means of quality control samples are 2.81–5.76%, 3.15–6.01%, 1.61–6.05% and 2.70–3.69% at concentrations of 0.5, 1, 5 and 40 ng/mL, respectively. The overall (inter-day) precision was 5.88%, 8.32%, 10.74% and 3.51% at concentration of 0.5, 1, 5 and 40 ng/mL, respectively. The accuracy of the assay as assessed by the relative error of measured and theoretical concentrations of rifaximin ranged between -0.02% to 5.40% for all quality control samples. The recovery (extraction efficiency) of rifaximin from human plasma was 70.6% ± 6%, 73.7% ± 2% and 83.5% at 1, 5 and 50 ng/mL, respectively. The recovery of rifaximin from human plasma was 76.3% ± 3% at a concentration of 20 ng/mL. Rifaximin was shown to be stable in human plasma at ambient temperature for at least 24 hours, and also after three freeze/thaw cycles. Additionally, extracts were demonstrated to be stable for at least 20 days after storage at +4 °C. The HPLC methods had a linear range of 0.5 to 40 ng/mL. The lower limit of quantitation was either 0.5 or 1 ng/mL. The % coefficient of variation (CV) at the LLOQ was 7.1% and 3.5% for plasma and urine, respectively, and <6% and <5% at above the LLOQ.

What Dissolution method and specification is proposed for release and stability testing?

The dissolution method and specification proposed by the sponsor for the release and stability testing of the drug product is as follows

Dosage Form	Tablets
Strength	200 mg Rifaximin
Apparatus Type	/
Medium	/
Medium Volume	/
Speed	/
Temperature	/
Proposed dissolution specification	Q = 1 at 1
The media was selected because	/

The sponsor used the above method to evaluate the comparative dissolution profiles of rifaximin tablets 200 mg used in the pivotal phase III study (study RFX -ID-9801, Lot 99002), a lot (Lot F0758A002) of at least 1 of the proposed commercial size manufactured at the proposed commercial site and 1 other lots as indicated in the table below

Table 22 The following table provides the lot used in comparative dissolution analyses

Lot	Use
4492	Clinical Study RFX9701 (N9001)
99002	Clinical Study RFX9801 (N9004)
6814	Primary Stability
F0758-002	Lot on Stability

Table 23 Dissolution Results in

Time (min)	Lot 99002		Lot 4992		Lot 6814		Lot F0758-002	
	% Dis-solved	%RSD	% Dis-solved	%RSD	% Dis-solved	% RSD	% Dis-solved	%RSD
20	/	6.2	/	7.5	/	4.9	/	5.5
40	/	7.2	/	6.9	/	2.8	/	4.8
60	/	4.6	/	6.5	/	2.1	/	3.9
80	/	3.2	/	6.7	/	3.8	/	4.0

Table 24 Using Lot 99002 as reference, the following similarity factors were calculated

Comparison	
Lot 99002 vs Lot 4992	85.1
Lot 99002 vs Lot 6814	87.5
Lot 99002 vs Lot F0758002	84.7

The sponsor submitted additional dissolution information during the review period (on 8/5/02). This information compared the dissolution of lot (99002) used in the pivotal safety and efficacy study (Study RFID 9801) with commercial lots using the sponsor's proposed method. The following is average dissolution profiles in the proposed media using the proposed method and the f2 calculations.

Table 25 Comparative Dissolution Lot Usage

Lot No	Manufacturer	Lot Size	Manufacture Date	Usage
99002			November 1998	RFID9801 ^a
			RFPK1001 ^b	
			RFPK1002 ^c	
F0982 001			December 2001	RFID3001 ^d
			RFPK1001	
			RFPK1002	
C2F0051			June 2002	Process validation

^aRFID9801 Phase 3 study supporting safety and efficacy of rifaximin

^bRFPK1001 Comparative bioavailability study

^cRFPK1002 distribution study in normal volunteers

^dRFPK3001 Phase 3 study supporting safety and efficacy of rifaximin

^eCommercial manufacturing site

Table 26 Dissolution Data pH - Media (% Rifaximin Dissolved ± Standard Deviation)

Lot	Time (minutes)
99002	
F0982 001	
F2C0051	
F2C0052	
F2C0053	

Table 27 Dissolution Profile Comparisons Using the f_2 (similarity) Metric^a

Lots Tested ^b
F0982 001 vs 99002
C2F0051 vs 99002
C2F0052 vs 99002
C2F0053 vs 99002

For the f_2 metric data from only the _____ time points were used
 In all comparisons the reference lot number was Lot 99002

The sponsor's rationale for selecting the media is acceptable _____

General Comments

The sponsor provided sufficient information to indicate systemic exposure is minimal. Even when a high fat meal increased the exposure to rifaximin, the increase was minimal and may not be clinically significant. However, the data provided in the submission only address the question of systemic absorption in either normal subjects or patients with conditions other than diarrhea. In general, rifaximin pharmacokinetics has not been systematically evaluated in special populations. There were insufficient pharmacokinetic data to assess the level of systemic absorption of rifaximin that might occur in patients with traveler's diarrhea. The sponsor should therefore provide data that evaluates the level of systemic absorption of rifaximin in patients with diarrhea. The effect of renal impairment on the excretion of rifaximin was not evaluated and is not known, however, very little drug (<1% of an oral dose) is excreted renally. A formal hepatic impairment pharmacokinetic study was not conducted, although in a multiple dose study in patients with cirrhosis and mild to moderate encephalopathy, who received regimens of 600, 1200 and 2400 mg/day in three divided doses for 7 days, rifaximin plasma and urine concentrations were not appreciably different than in healthy normal subjects dosed in other studies. Exposure in children was not evaluated and is not known. A study to determine the exposure in children is being requested for the applicant to obtain pediatric exclusivity via the pediatric written request process. Exposure evaluation in various subjects with different ethnic origin and gender was not submitted and is not known. However, studies that included male and female subjects did not appear to indicate differences in exposure due to gender.

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/s/

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