CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-361

ADMINISTRATIVE DOCUMENTS

From 12/21/01 Submission

N2307

RIFAXIMIN

1 7 ITEM 13 PATENT INFORMATION

ITEM 13 Patent Information on Any Patent Which Claims the Drug

In accordance with 21 USC 355(b) or (c), Table 1 summarizes the patent information on any patent that claims the use of the drug

Table 1 Patent Information

Patent Number	Title	Type	Assignee	Agent	Issue/ Expiration Dates
5,886,002	Use of Rifaximin and of Pharmaceutical Compositions Containing It in the Treatment of the Diarrhoea from Cryptosporidiosis	Use	Alfa Wassermann	Not applicable	Mar 23, 1999/ Jan 26, 2018

N2308

RIFAXIMIN

1 8 ITEM 14 PATENT CERTIFICATION AND CLAIMED EXCLUSIVITY STATEMENT

ITEM 14. Patent Certification With Respect To Any Patent Which Claims the Drug

In accordance with 21 USC 355(b)(2) or (j)(2)(A), the following contains a Patent Certification statement and New Drug Exclusivity Statement for the drug No patents are listed in the FDA's Orange Book

PATENT CERTIFICATION
NDA 21-361
RIFAXIMIN

The undersigned declares that Patent Number 5,886,002 covers a method of use of rifaximin tablets This product is the subject of this application, NDA 21-361, for which approval is being sought Salix Pharmaceuticals, Inc has a licensing agreement with the Patent Owner for Patent Number 5,886,002

Lorin K Johnson, Ph D
Senior Vice President and Chief Scientific Officer

11/28/01
Date

NEW DRUG PRODUCT EXCLUSIVITY
NDA 21-361
RIFAXIMIN

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act, 21 CFR 314 50(j)(3), and 21 CFR 314 108 (b)(2), Salix Pharmaceuticals, Inc is requesting a five-year period of marketing exclusivity from the approval of the referenced NDA based on the following

1 The active ingredient in the drug product, rifaximin, has not been approved in another drug product in the United States either as a single entity or as part of a combination drug product, and
2 The active ingredient, rifaximin, has not been previously marketed in a drug product in the United States
3 The FDA's Orange Book does not list rifaximin as an approved or discontinued drug product in the United States

Lorin K Johnson, Ph D
Senior Vice President and Chief Scientific Officer

11/28/01
Date

EXCLUSIVITY SUMMARY FOR NDA # **21-361** SUPPL # n/a

Trade Name **Xifaxan** Generic Name **rifaximin**

Applicant Name **Salix Pharmaceuticals, Inc** HFD# **590**

Approval Date If Known **May 25, 2004**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1 An exclusivity determination will be made for all original applications, and all efficacy supplements Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /**X**/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no ")

YES /**X**/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data

N/A

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__5 years__

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

___N/A_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT

2 Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade)

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1 Single active ingredient product

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e g , this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce

an already approved active moiety

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s)

NDA# N/A N/A

NDA# _____ _____

NDA# _____ _____

2 Combination product

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes " (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved)

YES /___/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s)

NDA# N/A N/A

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (Caution The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities) IF "YES" GO TO PART III

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant " This section should be completed only if the answer to PART II, Question

1 or 2 was "yes "

1 Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a) If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8

2 A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i e , information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO

YES /___/ NO /___/

If yes, explain

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval

---

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section

3 In addition to being essential, investigations must be "new" to support exclusivity The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i e , does not redemonstrate something the agency

considers to have been demonstrated in an already approved application

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no ")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i e , the investigations listed in #2(c), less any that are not "new")

_____ _____

_____ _____

4 To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study

a) For each investigation identified in response to question 3(c) if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not

be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES /___/ NO /___/

If yes, explain _____

_____

Andrei Nabakowski, Pharm D May 7, 2004
Regulatory Project Manager
FDA/CDER/ODE-IV/DSPIDP

Mark Goldberger, M D , M P H May 25, 2004
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Form OGD-011347 Revised 05/10/2004

cc
Archival NDA
HFD-590/Division File
HFD-590/Andrei Nabakowski
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T Crescenzi

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

/s/

Andrei Nabakowski
5/25/04 11 15 38 AM
NDA 21-361/Rifaximin Exclusivity Checklist

Edward Cox
5/25/04 05 26 34 PM
for Mark J Goldberger, MD MPH

From 12/21/01 Submission

N2309

RIFAXIMIN

1 10 ITEM 16 DEBARMENT CERTIFICATION

ITEM 16. Debarment Certification

A debarment certification is attached.

DEBARMENT CERTIFICATION
NDA21-361
RIFAXIMIN

Salix Pharmaceuticals, Inc hereby certifies that it did not and will not use in any capacity the services of any persons debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act in connection with this application (NDA 21-361)

11/28/01

Lorin Johnson, Ph D
Sr Vice President and Chief Scientific Officer

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # 21-361 Supplement Type (e g SE5) N/A Supplement Number N/A

Stamp Date November 25, 2003 Action Date May 26, 2004

HFD 590 Trade and generic names/dosage form Xifaxan (rifaximin) Tablets 200 mg

Applicant Salix Pharmaceuticals, Inc Therapeutic Class Antimicrobial

Indication(s) previously approved None

Each approved indication must have pediatric studies Completed, Deferred, and/or Waived

Number of indications for this application(s) 1

Indication #1 For use in patients ≥ 12 years old with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*

Is there a full waiver for this indication (check one)?

- ☐ Yes Please proceed to Section A
- X No Please check all that apply X Partial Waiver X Deferred ____Completed
  NOTE More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary

Section A Fully Waived Studies

Reason(s) for full waiver

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other _____

If studies are fully waived then pediatric information is complete for this indication If there is another indication please see Attachment A Otherwise this Pediatric Page is complete and should be entered into DFS

Section B Partially Waived Studies

Age/weight range being partially waived

Min	X	kg	mo	yr 0	Tanner Stage
Max	X	kg	mo	yr 3	Tanner Stage

Reason(s) for partial waiver

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- X Adult studies ready for approval
- ☐ Formulation needed
- X Other Pathogens which cause diarrhea in this age group are typically viral, so rifaximin not indicated

If studies are deferred proceed to Section C If studies are completed proceed to Section D Otherwise this Pediatric Page is complete and should be entered into DFS

Section C Deferred Studies

Age/weight range being deferred

Min	**X**	**kg**	**mo**	**yr 3**	**Tanner Stage**
Max	**X**	**kg**	**mo**	**yr 11**	**Tanner Stage**

Reason(s) for deferral

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other _____

Date studies are due (mm/dd/yy) 05/01/2009

If studies are completed proceed to Section D Otherwise this Pediatric Page is complete and should be entered into DFS

Section D Completed Studies

Age/weight range of completed studies

Min		**kg**	**mo**	**yr**	**Tanner Stage**
Max		**kg**	**mo**	**yr**	**Tanner Stage**

Comments

If there are additional indications please proceed to Attachment A Otherwise this Pediatric Page is complete and should be entered into DFS

This page was completed by

{See appended electronic signature page}

Andrei E Nabakowski, Pharm D
Regulatory Project Manager
FDA/CDER/ODE-IV/DSPIDP

cc **NDA 21-361**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337

(revised 12-22-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

/s/

Andrei Nabakowski
5/25/04 10 25 35 AM
CSO
NDA 21-361/Rifaximin Peds Page

Deputy Office Director Review
NDA 21-361
Salix's Rifaximin Tablets for Travelers' Diarrhea

NDA#	21-361
Applicant	Salix Pharmaceuticals, Inc
Drug Name	rifaximin
Proprietary Name	Xifaxan™
Date of Submission	11/25/2003
CDER stamp date	11/26/2003
PDUFA goal date	5/26/04
Formulation	Tablet (200 mg)
Proposed indication	Travelers' diarrhea
Proposed regimen	one 200 mg tablet taken orally three times daily for three days

Recommended Regulatory Action Approval

Background
Rifaximin is a rifamycin derivative that when administered orally is minimally absorbed Other member of the rifamycin class include rifampin, rifabutin, and rifapentine In NDA 21-361, the Applicant has investigated the use of rifaximin tablets administered orally for the treatment of travelers' diarrhea

Rifaximin (a 200 mg tablet and granules for suspension) was first approved in Italy in 1985 (launched in 1987) for several indications involving the treatment of gastrointestinal infections or flora Subsequent to approval in Italy, approvals have been granted in twelve other countries (Argentina, Bulgaria, Columbia, The Czech Republic, Hungary, Mexico, Lebanon, Pakistan, Romania, Spain, Venezuela, and Vietnam) No marketing authorizations have been rejected for safety reasons

Other agents that are indicated for the treatment of either infectious diarrhea or travelers' diarrhea include Cipro® (ciprofloxacin), Bactrim® (trimethoprim and sulfamethoxazole), and Septra® (trimethoprim and sulfamethoxazole), and Furoxone® (furazolidone) These agents are all systemically absorbed There are also over-the-counter agents that are available for the symptomatic treatment of diarrhea including anti-motility agents such as Imodium® A-D (loperamide hydrochloride) and agents such as Pepto-Bismol® which contains bismuth subsalicylate which is believed to work in the symptomatic treatment of diarrhea via its antisecretory and possibly its antimicrobial and anti-bacterial toxin effects

NDA 21-361 was originally submitted on December 21, 2001 (CDER stamp date December 26, 2001) and received an approvable letter on October 25, 2002

The letter asked for an additional study of travelers' diarrhea at the proposed dose of 200 mg po TID Additional data from patients with common pathogens in travelers' diarrhea other than just enterotoxigenic *E coli* (ETEC) (e g *Campylobacter* spp , *Salmonella* spp , *Shigella* spp) The letter also asked for additional data on absorption of rifaximin in patients with travelers' diarrhea and further evaluation of the potential for drug-drug interactions The letter also asked for additional data on particle size distribution, impurities and degradants in the drug product, and stability data The Applicant re-submitted NDA 21-361 on November 25, 2003 (CDER stamp date November 26, 2003)

Chemistry
The chemistry deficiencies noted in the approvable letter of October 25, 2002 have been satisfactorily addressed and the chemist is recommending approval from the standpoint of chemistry

Pharmacology/Toxicology
There are no new pharmacology/toxicology studies in the re-submission Rifaximin is classified as pregnancy category C The review also notes the minimal systemic exposure of rifaximin when administered orally in pre-clinical and clinical studies

Microbiology
Rifamycins act by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial protein synthesis Although in *in vitro* studies, rifaximin showed activity against *Shigella*, *Salmonella*, *Aeromonas*, and *E coli* with MICs ranging 8-64 µg/mL, from the clinical microbiology data obtained from patients in the clinical studies, clear evidence of microbiologic activity was not demonstrated

Clinical Pharmacology / Biopharmaceutics
In the re-submission the applicant has provided the report from a clinical pharmacology study evaluating the pharmacokinetics of rifaximin in patients with enteric infection The results of this study show that rifaximin is minimally absorbed from the gastrointestinal tract In addition, results from drug interaction studies were also provided that showed that rifaximin does not alter the pharmacokinetics of oral contraceptives and midazolam administered either orally or intravenously There are no outstanding Clinical Pharmacology / Biopharmaceutics issues for NDA 21-361

Clinical / Statistical
The Applicant provided data from one phase II (RFID9601) and three phase III controlled clinical studies (RFID9701, RFID9801, and RFID3001) of rifaximin for the treatment of travelers' diarrhea (Table 1) Study RFID9801 and RFID3001 both utilized the proposed dosage regimen of rifaximin 200 mg po TID for 3 days duration

Table 1 Controlled Studies of Rifaximin for Travelers' Diarrhea

Study Number	Study Title	Design	Treatment Arms	Dose and Duration	No of Patients Enrolled
RFID9601	A Randomized Double Blind Study of 3 Dosing Regimens of Rifaximin to a Standard TMP/SMX Regimen in the Treatment of Travelers Diarrhea	Randomized Double-blind	Rifaximin	200 mg po TID x 5 days	19
			Rifaximin	400 mg po TID x 5 days	19
			Rifaximin	600 mg po TID x 5 days	19
			TMP/SMX	160/800 mg po BID x 5 days	19
RFID9701	Rifaximin Double-blind Randomized Trial Comparing Rifaximin to a Standard Regimen of Ciprofloxacin in the Treatment of Travelers Diarrhea	Randomized Double-blind Double-dummy	Rifaximin	400 mg po BID x 3 days	93
			Ciprofloxacin	500 mg po BID x 3 days	94
RFID9801	A Randomized Double-Blind Parallel Comparative Placebo-Controlled Study of Rifaximin at 600 mg/day (200 mg TID) and 1200 mg/day (400 mg TID) in the Treatment of Bacterial Infectious Diarrhea in Travelers	Randomized Double-blind	Rifaximin	200 mg po TID x 3 days	125
			Rifaximin	400 mg po TID x 3 days	126
			Placebo	x 3 days	129
RFID3001	A Randomized Double-Blind Multi-Center Comparative Study of Rifaximin vs Placebo vs Ciprofloxacin (Cipro®) in the Treatment of Travelers Diarrhea	Randomized (2 1 1) Double-blind	Rifaximin	200 mg po BID x 3 days	197
			Ciprofloxacin	500 mg po BID x 3 days	101
			Placebo	x 3 days	101

Source Adapted from Table 27 from p 62 of the Overall Summary of the Application NDA 21-361 for the original NDA submission with addition of subsequent information

Efficacy Results

Study RFID 9601 was a randomized, double blind phase II dose ranging study comparing three doses of rifaximin (200 mg, 400 mg, 600 mg po TID) to TMP/SMX (trimethoprim sulfamethoxazole, 160/800 mg) po BID, all administered for 5-days This study enrolled slightly fewer than twenty patients in each treatment group The mean age of the study population was approximately 25 years of age The study was designed to look at time to last unformed stool (TLUS) for each of the study arms The mean and median TLUS for the four treatment groups were not markedly different across the doses studied, considering the small number of patients enrolled (Table 2)

Table 2 Study RFID9601 - Mean and Median TLUS by Treatment Group

Time to Last Unformed Stool (hours)	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
Mean ± SD	37 ± 37	39 ± 24	53 ± 44	56 ± 50
Median	26	41	35	47

Source Adapted from Table 38 from Dr Alivisatos s MOR for the original NDA submission

Study RFID9701 was a randomized, double blind phase III study comparing rifaximin 400 po BID for 3 days to ciprofloxacin 500 mg po BID administered for 3 days The mean age of the study population was approximately 25 years of age The primary endpoint was time to last unformed stool (TLUS) The median TLUS for rifaximin 400 mg po BID was 25 7 hours (95% confidence interval (CI) 20 9-38 0) and for ciprofloxacin the TLUS was 25 0 hours (95% CI 18 5-35 2) Rifaximin at the dose of 400 mg po BID was found to be non-inferior to ciprofloxacin 500 mg po BID

Study RFID9801 was a randomized, double blind phase III study comparing placebo to rifaximin 200 mg po TID and rifaximin 400 mg po TID administered for 3 days The mean age of the study population was almost 30 years of age The primary endpoint was time to last unformed stool (TLUS) The median TLUS for placebo was 58 6 hours compared to rifaximin 200 mg po TID at 32 5 hours and rifaximin 400 mg po TID at 30 1 hours (Table 3) The TLUS for rifaximin at the doses of 200 mg po TID and 400 mg po TID were both found to be superior to placebo

Table 3 Study RFID9801 - Time to Last Unformed Stool by Treatment Arm - ITT

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
TLUS (hours) (Kaplan-Meier Estimates)			
Median TLUS	58 6	32 5	30 1
95% CI of Median TLUS	(45 5, 79 5)	(28 4, 43 4)	(22 7, 41 8)
P-Value (Wald Statistic)		0 0002	0 0001
97 5% CI for Hazard Ratio		(1 26, 2 50)	(1 30, 2 56)

Source Table 9801-2 from Dr Cheryl Dixon s Statistical Review for the original NDA submission

Patients underwent microbiologic evaluations at baseline and again at the post-treatment visit 24 to 48 hours after completing therapy In study RFID9801 comparisons of microbiologic cure rates did not distinguish the antimicrobial effects of rifaximin compared to placebo

The Agency's statistician performed an analysis to examine TLUS for patients with enterotoxigenic *E coli* (ETEC) (Table 4) This analysis found that there was a trend toward an earlier TLUS in patients receiving one of the rifaximin regimens compared to placebo

Table 4 Study RFID9801 – TLUS by Pathogen (MITT-type population)

Organism	TLUS (hours)		
	Placebo	Rifaximin 200 mg PO TID	Rifaximin 400 mg PO TID
ETEC	57 8 (n=54)	28 4 (n=53)	26 8 (n=45)

Source Adapted from Dr Dixon s Statistical Review Table 9801-5 for the original NDA submission

Study RFID 3001 was a randomized (2 1 1), double blind, phase III study comparing rifaximin 200 mg po TID vs ciprofloxacin 500 mg po BID vs placebo all administered for 3 days The primary endpoint was time to last unformed stool (TLUS) In the intent-to-treat population (ITT), the median TLUS for rifaximin 200 mg po TID was 32 0 hours compared to 65 5 hours for placebo and 28 8 hours for ciprofloxacin However, examination of the by center results revealed a treatment by center interaction Therefore the results were examined by center in the absence of pooling and the results were also examined excluding the two sites where the positive or negative control results were aberrant The results in the ITT population excluding the aforementioned two sites found a median TLUS of 23 9 hours for rifaximin, 65 5 hours for placebo, and 23 6 hours for ciprofloxacin (relative risk of rifaximin/placebo for TLUS was 2 17 (95% CI=1 44-3 27, p=0 0002) The median TLUS in the microbiological ITT (MITT) population was 40 3 hours for rifaximin, 48 3 hours for placebo, and 28 3 hours for ciprofloxacin An analysis excluding the two sites with aberrant results for the positive or negative control showed a median TLUS in the MITT population of 23 95 hours for rifaximin, 61 9 hours for placebo, and 20 6 hours for ciprofloxacin Analyses of "Wellness" in patients with fever, blood in the stool, and fever and blood in the stool and analysis of TLUS in patients with blood in the stool showed similar response rates for rifaximin and placebo

In addition to the controlled studies, results from a phase 1 open-label, pharmacokinetic study that enrolled 15 adult subjects that were challenged with *Shigella flexneri* 2a and treated with rifaximin were also reported Rifaximin therapy was initiated at the point in time when a patient met the protocol definition of diarrhea Thirteen of the 15 patients developed diarrhea or dysentery and were treated with rifaximin Although this open-label challenge trial was not adequate to assess the effectiveness of rifaximin in the treatment of Shigellosis, the following observations were noted Eight subjects received rescue treatment with ciprofloxacin either because of lack of response to rifaximin treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1) Five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse

Collectively the studies support the efficacy of rifaximin in the treatment of travelers' diarrhea due to non-invasive strains of *E coli* at a dose of 200 mg po TID for three days in patients $\geq$ 12 years of age Given the findings in patients

with fever and/or blood in the stool at baseline the product labeling should inform patients about the lack of effect in the treatment of patients with fever or blood in the stool Patients who develop worsening symptoms or who fail to respond at 24-48 hours should seek further medical attention for re-evaluation The label should also inform about the lack of efficacy in the treatment of travelers' diarrhea due to *Campylobacter jejuni* and the lack of data to support efficacy in the treatment of travelers' diarrhea due to *Shigella* spp and *Salmonella* spp

Safety Results

A total of 593 subjects (data for 591 unique individuals) received rifaximin at doses between 600 mg and 1800 mg orally daily A total of 320 patients received rifaximin 200 mg po TID for three days in the phase III placebo controlled studies RFID9801 and RFID3001 The frequency of adverse events in patients in these two studies is summarized in Table 5

Table 5 All Adverse Events Occurring in ≥2% of Patients in the Rifaximin 600 mg/day or Placebo Groups (RFID9801 & RFID3001)

	Number (%) of Patients	
System Organ Class MedDRA Preferred Term	**Rifaximin 600 mg/day (N = 320)**	**Placebo N = 228**
Any Adverse Event	142 (44 4%)	122 (53 5%)
Gastrointestinal Disorders	94 (29 4%)	97 (42 5%)
Flatulence	36 (11 3%)	45 (19 7%)
Abdominal Pain NOS	23 (7 2%)	23 (10 1%)
Rectal Tenesmus	23 (7 2%)	20 (8 8%)
Defecation Urgency	19 (5 9%)	21 (9 2%)
Nausea	17 (5 3%)	19 (8 3%)
Constipation	12 (3 8%)	8 (3 5%)
Vomiting NOS	7 (2 2%)	4 (1 8%)
Diarrhea NOS	2 (0 6%)	11 (4 8%)
General Disorders and Administration Site Conditions	17 (5 3%)	17 (7 5%)
Pyrexia	10 (3 1%)	10 (4 4%)
Nervous System Disorders	38 (11 9%)	30 (13 2%)
Headache	31 (9 7%)	21 (9 2%)
Dizziness	3 (0 9%)	7 (3 1%)

Source Adapted from Applicant s Table 21 from Vol 31 p 243 of the November 2003 re-submission

Adverse event rates for rifaximin were similar to (and in most categories, lower than) those for placebo Most of these adverse event reports represented symptoms of the underlying disease and did not appear specifically drug-related The Applicant reports that since the product was launched in Italy in 1987 and subsequently in 14 other countries only 11 patient reports of adverse events have been submitted, these included 5 cases of urticaria The remaining cases included single occurrences of agitation, syncope, headache, nausea, esophageal pain, and limb edema

Conclusions

The data provided within NDA 21-361 support the safety and efficacy of rifaximin 200 mg po TID for the treatment of travelers' diarrhea due to non-invasive strains of *E coli* in patients ≥ 12 years of age Given the findings in patients with fever and/or blood in the stool at baseline the product labeling should inform patients about the lack of effect in the treatment of patients with fever or blood in the stool Patients who develop worsening symptoms or who fail to respond at 24-48 hours should seek further medical attention The label should also inform about the lack of efficacy in the treatment of travelers' diarrhea due to *Campylobacter jejuni* and the lack of data to support efficacy in the treatment of travelers' diarrhea due to *Shigella* spp and *Salmonella* spp The recommended regulatory action is approval

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

/s/

Edward Cox
5/25/04 05 21 09 PM
MEDICAL OFFICER

Medical Team Leader's Memo
NDA 21-361
Salix's Rifaximin Tablets for Traveler's Diarrhea

Date October 21, 2002

From Edward M Cox, M D , M P H
Medical Team Leader (MTL), DSPIDP, HFD-590

Re Rifaximin tablets
Salix Pharmaceuticals, Inc
Submission date 12/21/01
CDER stamp date 12/26/01
PDUFA goal date 10/26/02
Proposed indication Traveler's diarrhea
Proposed dose and duration one 200 mg tablet taken three times daily for three days

MTL s Recommended Regulatory Action Approvable

Background

Rifaximin is a rifamycin derivative that when administered orally is minimally absorbed (based upon studies in patients with conditions other than infectious diarrhea) Other member of the rifamycin class include rifampin, rifabutin, and rifapentine In NDA 21-361, the Applicant has investigated the use of rifaximin tablets administered orally for the treatment of traveler's diarrhea Rifaximin is also currently being investigated as an agent for the treatment of hepatic encephalopathy

Rifaximin (a 200 mg tablet — was first approved in Italy in 1985 (launched in 1987) for several indications involving the treatment of gastrointestinal infections or flora Subsequent to approval in Italy, approvals have been granted in twelve other countries (Argentina, Bulgaria, Columbia, The Czech Republic, Hungary, Mexico, Lebanon, Pakistan, Romania, Spain, Venezuela, and Vietnam) No marketing authorizations have been rejected for safety reasons Since initial launch in Italy in 1987 followed by subsequent launches in other countries, there have been 19 spontaneous adverse events reported from 11 patients, the adverse events reported most frequently included urticaria (n=5, one case reported as serious) and two related adverse events, pruritis (n=1), and allergic dermatitis (n=1) Also reported were abdominal pain, agitation, syncope, headache, nausea, esophageal pain, and limb edema

Other members of the rifamycin class include rifampin, rifapentine, and rifabutin These are systemically available agents indicated for either the treatment of *Mycobacterium tuberculosis* or disseminated *Mycobacterium avium* complex disease Rifampin also carries an additional indication for the treatment of asymptomatic carriers of *Neisseria meningitidis* and authoritative infectious diseases references[1] also describe the off-label use of rifampin as adjunctive therapy in several types of bacterial infections (e g , infections with *Staphyloccuccus* spp involving prosthetic devices) Agents of the rifamycin class have been associated with hepatic toxicity, induction of the cytochrome P450 system, and drug interactions Rifampin and Rifapentine also include a precautionary statement regarding the association with exacerbations of porphyria (because of induction of delta amino levulinic acid synthetase) Rifabutin has been associated with uveitis in the setting of higher doses of rifabutin and/or in the setting of concomitant administration of interacting drugs Rifampin and rifabutin also include information on the adverse reactions of thrombocytopenia and leukopenia

Other agents that are indicated for the treatment of either infectious diarrhea or traveler's diarrhea include Cipro® (ciprofloxacin), Bactrim® (trimethoprim and sulfamethoxazole), and Septra® (trimethoprim and sulfamethoxazole), and Furoxone® (furazolidone) These agents are all systemically absorbed There are also over-the-counter agents that are available for the symptomatic treatment of diarrhea including anti-motility agents such as Imodium® A-D (loperamide hydrochloride) and agents such as Pepto-Bismol® which contains bismuth subsalicylate which is believed to work in the symptomatic treatment of diarrhea via its antisecretory and possibly its antimicrobial and anti-bacterial toxin effects

During the development of rifaximin, there were several meetings and communications that took place between the Agency and the Sponsor During these interactions, there were several items that were communicated to the company including that the application should

1 provide an adequate experience with the variety of bacterial pathogens that are typically associated with traveler's diarrhea (e g , *E coli* strains *Camplylobacter* spp , *Shigella* spp , non-typhi *Salmonella*)
2 provide sufficient data to support the proposed rifaximin dose of 200 mg po TID (The clinical studies employed several different doses across the studies)
3 provide data to support the comparability of the rifaximin formulations used in the clinical studies with the proposed to be marketed formulation

These issues, among others, were brought to the attention of the sponsor during a teleconference on 12/7/01 and were followed up with a FAX sent on 12/14/01

[1] Farr BM Rifamycins (Chapter 25) in *Mandell, Douglas and Bennett s Principles and Practices of Infectious Diseases* 5th Edition Mandell GL, Bennett JE Dolin R Eds Churchill Livingstone 2000 pp 348-361

To address issues one and two above, it was suggested that Salix perform an additional three-arm clinical study (rifaximin, placebo, and active control – ciprofloxacin) prior to the submission of their NDA application At this time, this additional study is currently on-going

Applicant's Proposed Indication

INDICATIONS AND USAGE *LUMENAX Tablets are indicated for the treatment of patients (≥12 years of age) with traveler's diarrhea caused by Escherichia coli*

Selected Key Microbiologic, Biopharmaceutics, and Pharm/Tox Data

Rifamycins act by binding to the beta the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial protein synthesis The MIC_{50} and MIC_{90} ranges for rifaximin for the bacterial organisms that the Applicant proposes to include in the Indication and Usage section are shown in Table 1

Table 1 MIC_{90} Ranges for Selected Bacterial Pathogens

Organism	Range of MIC_{50}s for Strains Tested (mcg/mL)	Range of MIC_{90}s for Strains Tested (mcg/mL)
Escherichia coli strains*	8 – 64	16 –128
Campylobacter strains	32 – >200	64 – 256**
Salmonella spp	32 – 64	50 – 128
Shigella spp	4 – 64	8 – 128
Vibrio spp	16 –100	32 – 128

Source of Data Dr Dionne s Microbiologist s review Table A p 4
*The range of MIC_{90}s presented represent the range of the MIC_{90}s for the individual strains of enterotoxigenic *E coli* and enteroaggregative *E coli* that were tested For additional details please see Dr Pete Dionne s microbiologist s review
** The MIC_{90} for one of the groups of strains tested was listed as >200 mcg/mL

A study that measured levels of rifaximin in stool in adults with infectious diarrhea treated with rifaximin 800 mg daily for three days found that on the first day post treatment the mean stool concentrations (mcg/gram of stool) (+/- SE) were 7962 +/- 4151 mcg/g Rifaximin stool concentrations then declined over the next five to seven after treatment had been completed

MO Comment Despite their wide variability, these levels do provide some information regarding levels achieved in stool However, it isn't

clear what the stool levels mean with regards to the levels achieved at the active site of infection Some of the pathogens in the proposed indication are facultative intracellular organism which are capable of producing invasive disease In such situations, concentrations of drug in the intestinal lumen may be less germane than the tissue concentrations achieved at the site of infection

In studies enrolling healthy subjects receiving a single oral dose of rifaximin of 400 mg, mean plasma concentrations of 13 0 –20 6 ng/mL were achieved Food was found to increase the plasma concentrations of rifaximin detected by a factor of 2 9 to 2 7 times for the parameters of C_{max} and AUC While there is some data on systemic absorption in patients with Crohn's disease and ulcerative colitis, the levels of systemic absorption of rifaximin was not studied in patients with infectious diarrhea, a population of individuals in whom alterations in bowel wall integrity could lead to increased absorption Based upon findings from the pre-clinical studies, the potential for toxicity from acute exposure to higher doses or chronic low-level exposure to rifaximin may exist However, these toxicities should be unlikely to manifest in the setting of minimal absorption during short duration therapy using the proposed dose of 200 mg po TID

MO Comment Additional information on the systemic absorption of rifaximin in patients with infectious diarrhea (ID) would be of value in understanding the levels of drug systemically absorbed in patients with ID Such information would be helpful to clinicians considering using rifaximin in patients who may be receiving other drugs metabolized by the cytochrome P450 system or in special populations (e g , pregnant females) In the absence of such information regarding the systemic levels of rifaximin achieved in patients with infectious diarrhea, healthcare practitioners may not have all of the information that they need to optimally utilize rifaximin

Clinical Safety and Efficacy Data

The Applicant provided data from one phase II (RFID9601) and two phase III (RFID9701 and RFID9801) studies of rifaximin for the treatment of traveler's diarrhea (Table 2) Study 9801 was the only study that examined the proposed dosage regimen of rifaximin 200 mg po TID for 3 days duration

Table 2 Controlled Studies of Rifaximin for Traveler's Diarrhea

Study Number	Title	Design	Treatment	Dose and Duration	No of Patients Enrolled
RFID9601	A Randomized Double Blind Study of 3 Dosing Regimens of Rifaximin to a Standard TMP/SMX Regimen in the Treatment of Traveler s Diarrhea	Randomized Double-blind	Rifaximin	200 mg po TID x 5 days	19
			Rifaximin	400 mg po TID x 5 days	19
			Rifaximin	600 mg po TID x 5 days	19
			TMP/SMX	160/800 mg po BID x 5 days	19
RFID9701	Rifaximin Double-blind Randomized Trial Comparing Rifaximin to a Standard Regimen of Ciprofloxacin in the Treatment of Traveler s Diarrhea	Randomized Double-blind Double-dummy	Rifaximin	400 mg po BID x 3 days	93
			Ciprofloxacin	500 mg po BID x 3 days	94
RFID9801	A Randomized Double-Blind Parallel Comparative Placebo-Controlled Study of Rifaximin at 600 mg/day (200 mg TID) and 1200 mg/day (400 mg TID) in the Treatment of Bacterial Infectious Diarrhea in Traveler s	Randomized Double-blind	Rifaximin	200 mg po TID x 3 days	125
			Rifaximin	400 mg po TID x 3 days	126
			Placebo	--	129

Source Adapted from Table 27 from p 62 of the Overall Summary of the Application NDA 21-361

Efficacy Results

Study RFID 9601 was a randomized, double blind phase II dose ranging study comparing three doses of rifaximin (200 mg, 400 mg, 600 mg po TID) to TMP/SMX (trimethoprim sulfamethoxazole, 160/800 mg) po BID, all administered for 5-days This study enrolled slightly fewer than twenty patients in each treatment group The mean age of the study population was approximately 25 years of age The study was designed to look at time to last unformed stool (TLUS) for each of the study arms The mean and median TLUS for the four treatment groups were not markedly different across the doses studied, considering the small number of patients enrolled (Table 3)

Table 3 Study RFID9601 - Mean and Median TLUS by Treatment Group

Time to Last Unformed Stool (hours)	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
Mean ± SD	37 ± 37	39 ± 24	53 ± 44	56 ± 50
Median	26	41	35	47
Source Adapted from Table 38 from Dr Alavisatos s MOR				

Study RFID9701 was a randomized, double blind phase III dose study comparing rifaximin 400 po BID for 3 days to ciprofloxacin 500 mg po BID administered for 3 days The mean age of the study population was approximately 25 years of age The primary endpoint was time to last unformed stool (TLUS) The median TLUS for rifaximin 400 mg po BID was 25 7 hours (95% confidence interval (CI) 20 9-38 0) and for ciprofloxacin the TLUS was 25 0 hours (95% CI 18 5-35 2) Rifaximin at the dose of 400 mg po BID was found to be non-inferior to ciprofloxacin 500 mg po BID

Study RFID9801 was a randomized, double blind phase III study comparing placebo to rifaximin 200 mg po TID and rifaximin 400 mg po TID administered for 3 days The mean age of the study population was almost 30 years of age The predominant race enrolled in the study was "white" (approx 85%) The primary endpoint was time to last unformed stool (TLUS) The median TLUS for placebo was 58 6 hours compared to rifaximin 200 mg po TID at 32 5 hours and rifaximin 400 mg po TID at 30 1 hours (Table 4) The TLUS for rifaximin at the doses of 200 mg po TID and 400 mg po TID were both found to be superior to placebo

Table 4 Study RFID9801 - Time to Last Unformed Stool by Treatment Arm - ITT

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
TLUS (hours) (Kaplan-Meier Estimates)			
Median TLUS	58 6	32 5	30 1
95% CI of Median TLUS	(45 5, 79 5)	(28 4, 43 4)	(22 7, 41 8)
P-Value (Wald Statistic)		0 0002	0 0001
97 5% CI for Hazard Ratio		(1 26, 2 50)	(1 30, 2 56)
Source Table 9801-2 from Dr Cheryl Dixon s Statistical Review			

Patients underwent microbiologic evaluations at baseline and again at the post-treatment visit 24 to 48 hours after completing therapy In study RFID9801 comparisons of microbiologic cure rates did not distinguish the antimicrobial effects of rifaximin compared to placebo The microbiologic cure rates for pathogens isolated from more than 2 patients in at least one treatment arm in study RFID9801 are summarized in Table 5

Table 5 Microbiological Cure Rate for Selected Pathogen* (Study RFID9801)

Pathogen	Placebo		Rifaximin 200 mg TID		Rifaximin 400 mg TID	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	54	40/54 (74%)	54	38/54 (70%)	41	27/41 (66%)
Shigella sonnei	2	2/2 (100%)	2	2/2 (100%)	1	1/1 (100%)
Shigella flexneri	0	0	2	1/2 (50%)	1	0/1 (0%)
Salmonella Group C1	1	1/1 (100%)	2	1/2 (50%)	4	3/4 (75%)
Salmonella Group C2	1	1/1 (100%)	0	0	3	1/3 (33%)
Campylobacter jejuni	1	0/1 (0%)	2	1/2 (50 0%)	0	0
Entamoeba histolytica	1	1/1 (100%)	1	1/1 (100%)	3	2/3 (67%)
Giardia lamblia	4	3/4 (75%)	6	4/6 (67%)	3	1/3 (33%)
Cryptosporidium parvum	11	7/11 (64%)	18	12/18 (67%)	14	4/14 (29%)
TOTAL*	79	59/79 (75%)	88	61/88 (69%)	75	43/75 (57%)

Source adapted from Table 21 from Dr Alivisatos s MOR
*Only Pathogens isolated in 2 or more patients in at least one study arm are shown in this table
**The total includes cases not displayed in this table because there were fewer than two isolates in any one of the study arms

MO Comment Cultures obtained at baseline and 24 to 48 hours post-treatment may not be the appropriate time points to allow the activity of an active agent to be distinguished from placebo in a predominantly self-limited disease like traveler s diarrhea The Applicant currently has an on-going study which will obtain additional microbiologic data during treatment to investigate whether culturing at an earlier timepoint allows a difference in microbiologic response to be demonstrated between an active agent and placebo

The Agency's statistician performed an analysis to examine TLUS for patients with enterotoxigenic *E coli* (ETEC) and then for patients with *Cryptosporidium parvum* as their baseline isolates (Table 6) This analysis found that there was a trend toward an earlier TLUS in patients receiving one of the rifaximin regimens compared to placebo For patients with *Cryptosporidium parvum* isolated at baseline, the point estimate of TLUS was less than that of the placebo arm but greater than that observed for ETEC The TLUS result for patients with *Cryptosporidium* must be interpreted with great caution because only 6 of the 18 cases of *Cryptosporidium* in the rifaximin 200 mg po TID arm had *Cryptosporidium* as their sole pathogen Hence it is possible that the differences observed in TLUS in Table 6 for the *Cryptosporidium* cases may reflect the effect of rifaximin on the bacterial pathogen rather than the concurrently identified *Cryptosporidium*

Table 6 Study RFID9801 – TLUS by Pathogen (MITT-type population)

Organism	TLUS (hours)		
	Placebo	Rifaximin 200 mg PO TID	Rifaximin 400 mg PO TID
ETEC	57 8 (n=54)	28 4 (n=53)	26 8 (n=45)
Cryptosporidium	58 6 (n=11)	39 9 (n=18)	40 4 (n=14)

Source Adapted from Dr Dixon s Statistical Review Table 9801-5

The microbiological data from study RFID9701 which utilized a rifaximin dose of 400 mg po TID (a rifaximin dose different than the proposed dose of 200 mg po TID) did not provide evidence supporting the microbiologic efficacy of rifaximin In addition, these studies did not include a placebo arm, which compounds the difficulties in interpreting the microbiology data from these studies (Table 7)

Table 7 Study RFID9701 - Microbiological Cure Rate for Selected* Pathogens

Pathogen	Rifaximin 400 mg po bid		Ciprofloxacin 500 mg po bid	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	35	24/35 (69%)	36	30/36 (83%)
Shigella sonnei	4	3/4 (75%)	1	1/1 (100%)
Shigella flexneri	1	1/1 (100%)	5	4/5 (80%)
Salmonella Group C1	2	1/2 (50%)	3	2/3 (67%)
Salmonella Group C2	1	1/1 (100%)	2	2/2 (100%)
Campylobacter jejuni	2	2/2 (100%)	0	0
Cryptosporidium parvum	1	1/1 (100 %)	2	1/2 (50%)
TOTAL**	47	33/47 (70%)	51	41/51 (80%)

Source adapted from Table 33 from Dr Alivisatos s MOR
*Only Pathogens isolated in 2 or more patients in at least one study arm are shown in this table
**The total includes cases not displayed in this table because there were fewer than two isolates in any one of the study arms

The limited microbiologic data from study RFID9601 was not able to provide evidence in support of the microbiologic efficacy of rifaximin (data not shown)

Safety Results

The adverse events reported most frequently in the 400 rifaximin treated infectious diarrhea patients in the safety database were gastrointestinal adverse events that were also consistent with the symptoms of infectious diarrhea The adverse events occurring at a frequency of 2% or greater from study RFID 9801 are listed in Table 8 With the exception of headache, which appears to be occurring more frequently in rifaximin treated patients and may be more frequent with the higher rifaximin dose, the frequency of adverse events between

treatment arms is similar Also of note is a slightly higher rate for the adverse event of diarrhea in the placebo arm compared to the rifaximin arms The safety data from RFID9701 do not lead to any different conclusions regarding the adverse event profile of rifaximin compared to study RFID9801

Table 8 Adverse Events Occurring at ≥2% in Study RFID 9801

Adverse Event	Rifaximin 200 mg po TID (N=124)	Rifaximin 400 mg po TID (N=126)	Placebo (N=129)
Flatulence	32 (25 8)	36 (28 6)	42 (32 6)
Abdominal pain NOS	21 (16 9)	28 (22 2)	23 (17 8)
Tenesmus	19 (15 3)	14 (11 1)	19 (14 7)
Fecal incontinence	16 (12 9)	21 (16 7)	20 (15 5)
Nausea	16 (12 9)	20 (15 9)	18 (14 0)
Headache NOS	15 (12 0)	22 (17 5)	12 (9 3)
Pyrexia	8 (6 5)	7 (5 6)	9 (7 0)
Vomiting NOS	5 (4 0)	3 (2 4)	3 (2 3)
AST increased	4 (3 2)	0	4 (3 1)
Constipation	4 (3 2)	3 (2 4)	3 (2 3)
Chest pain NEC	2 (1 6)	1 (0 8)	1 (0 8)
Diarrhea NOS	2 (1 6)	2 (1 6)	8 (6 2)
Hematuria	2 (1 6)	0	1 (0 8)
Myalgia	2 (1 6)	0	0
Nasopharyngitis	0	2 (1 6%)	1 (0 8%)
Sunburn	2 (1 6)	0	0
Weakness	2 (1 6)	1 (0 8)	3 (2 3)
Blood in stool	1 (0 8)	0	2 (1 6)
Dizziness	1 (0 8)	5 (4 0)	5 (3 9)
Migraine NOS	1 (0 8)	0	2 (1 6)
Pain NOS	1 (0 8)	1 (0 8)	2 (1 6)
Fatigue	0	4 (3 2)	0
ALT increased	0	0	2 (1 6)
Back pain	0	1 (0 8)	2 (1 6)
Loose stool	0	0	2 (1 6)
Muscle cramps	0	1 (0 8)	2 (1 6)
Taste disturbance	0	0	2 (1 6)

Source Adapted from Table 32 from p 75 of the "Overall Summary of the Application NDA 21-361

Examining the composite adverse event data from the infectious diarrhea studies, in addition to the more frequent reporting of headache previously noted in RFID9801, fatigue and nasopharyngitis were reported more frequently in rifaximin treated patients than in the composite control arm (fatigue rifaximin 13/400 (3 3%) vs control1/241 (0 4%), nasopharyngitis rifaximin 8/400 (2 0%) vs control1/241 (0 4%) The reason for more frequent reporting of these adverse among patients receiving rifaximin (an agent that is expected to be minimally absorbed) is unclear

None of the rifaximin treated patients in the infectious diarrhea studies reported a serious adverse event One placebo treated patient from the infectious diarrhea studies [1/241 (0 4%) reported a serious adverse event (diarrhea)] No deaths

occurred in the infectious diarrhea studies Analysis of laboratory data did not reveal any marked differences between patients receiving rifaximin or comparator

The safety data from the infectious diarrhea studies was supplemented with data from patients receiving rifaximin for hepatic encephalopathy (HE) In the HE studies, patients received doses of rifaximin up to 1200 mg QD for 10 days or 800 mg TID for 7 days The adverse events reported in the HE studies were adverse events that were consistent with the patients' underlying liver disease and gastrointestinal adverse events (diarrhea and nausea)

Patient #28 from the hepatic encephalopathy studies died of hepatic failure He was a 63 year old Caucasian male with a diagnosis of cirrhosis due to alcohol and recurrent hepatic encephalopathy, grade 3 He had a history of gastric cancer 9 years prior to study enrollment and heart failure with onset of one month prior to study enrollment He was jaundiced at baseline The patient received only one day of study medication (rifaximin 1200 mg/day) and was removed from the study because of worsening of disease to grade 4 hepatic encephalopathy on study day 2, one day prior to death The cause of death was reported as hepatic failure that the investigator assessed this event as being unlikely related to study medication No concomitant medications were recorded

> **MO Comment** This patient's death occurred within 3 days of a single dose of rifaximin in the setting of marked underlying liver disease making factors other than rifaximin more likely to be causes of his liver failure

Conclusions

The results from study RFID9801 provide data from one adequate and well-controlled study that supports the clinical utility of rifaximin at the proposed dose of 200 mg po TID in shortening the time to last unformed stool in patients with traveler's diarrhea The other studies provide supportive data regarding the clinical activity of rifaximin using other rifaximin doses Additional anlayses of the data from RFID that examined TLUS in the subset of patients with ETEC at baseline provide some information in support of rifaximin's clinical activity in the treatment of ETEC associated traveler's diarrhea However, examination of data using the more traditional approach that employs follow-up cultures does not distinguish the antimicrobial activity of rifaximin from placebo for any of the pathogens evaluated The failure to demonstrate antimicrobial activity based upon culture data may be a study design issue that can be overcome by obtaining earlier follow-up cultures (as the Applicant is currently doing in their on-going clinical study) Data that defines the microbiologic spectrum of activity of rifaximin will help guide clinicians on when it would be appropriate to use rifaximin for the treatment of traveler's diarrhea Also important to note is that the severity of illness evaluated in the study RFID9801 was limited to patients appropriate for a placebo controlled study

The data presented from the safety database for rifaximin infectious diarrhea patients found a safety profile of adverse events that was similar to its comparators (placebo, ciprofloxacin, and TMP/SMX) There was a higher rate of fatigue, headache, and nasopharyngitis among the rifaximin treated patients Additional data from studies of patients with hepatic encephalopathy found an adverse event profile that was consistent with what would be expected for patients with liver disease

While there is some data from normal subjects and patients with Crohn's diasease and ulcerative colitis regarding the systemic absorption of rifaximin, it would also be helpful to study the levels of systemic absorption in the setting of bowel wall changes due to inflammatory enteritis due to traveler's diarrhea Additional pharmacokinetic data would help to address this question As noted in Dr Kumi's Biopharmaceutics review, an in vivo study to evaluate the potential of rifaximin to interact with other drugs metabolized by the cytochrome P450 system would help guide clinicians on the appropriate use of rifaximin Ideally such a study would be able to assess the effects of rifaximin on cytochrome P450 metabolism of both the liver and the gastrointestinal tract

As noted in Dr Sood's Chemist review, the data on particle size for the rifaximin lots used in the clinical studies as compared to the to-be-marketed formulation and a specification for particle size remain an outstanding issue that should be addressed

Recommendations for Additional Items to be Addressed

1 A second adequate and well-controlled clinical study that supports the safety and efficacy of rifaximin for the treatment of traveler's diarrhea should be performed
2 This second study should be designed to provide clinical microbiologic data from patients that will allow the comparative assessment of the microbiologic activity of rifaximin compared to placebo and the active comparator This data should clearly distinguish the microbiologic efficacy of rifaximin compared to placebo in order for the organism(s) to be included in the indication
3 [redacted]
4 The Applicant should also address the outstanding issue regarding the comparability of the rifaximin formulations used in the clinical studies to the to-be-marketed formulation and provide specifications for particle size

As noted in Dr Kumi's Biopharmaceutics review, it would also be of value to perform an *in vivo* drug interaction study to assess whether there is an interaction between cytochrome P450 3A4 substrates and rifaximin

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

---

/s/

Edward Cox
10/25/02 06 38 42 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE May 6, 2004

TO NDA 21-361/Rifaximin File

THROUGH Renata Albrecht, M D
Director, Division of Special Pathogen
and Immunologic Drug Products (DSPIDP) (HFD-590)

Mark Avigan, M D
Director, Division of Drug Risk Evaluation (HFD-430)

FROM Andrei Nabakowski, Pharm D , Regulatory Project Manager, DSPIDP

SUBJECT **Preapproval Safety Conference for NDA 21-361/Rifaximin**

The Division of Special Pathogen and Immunologic Drug Products and the Division of Drug Risk Evaluation have concurred that a Preapproval Safety Conference (PSC) is not required for NDA 21-361/Rifaximin

Rifaximin, a rifamycin derivative, has minimal systemic absorption and few adverse events were noted during the trials for NDA 21-361 These events were mild, self-limited and occurred with a frequency similar to the placebo The most frequently reported adverse events were gastrointestinal in nature and were symptoms of the underlying disease (e g , abdominal pain, fecal incontinence, flatulence, nausea and tenesmus) No deaths were reported in any of the studies Rifaximin has been approved in 13 foreign nations, and the overseas experience corresponds with the adverse event observations from the NDA 21-261 trials

MAPP 6010 1 "NDAs Preapproval Safety Conferences" lists six safety concern areas which the review division should inform DDRE about prior to approval None of these six items are of concern with rifaximin In addition, the MAPP states that the PSC should address any postmarketing safety issues which the division has identified DSPIDP has not identified any safety concerns which will require surveillance in postmarketing

Therefore, while Rifaximin is designated a New Chemical Entity, it is believed that it does not have the potential for new toxicities which have not been observed during clinical trials or as an approved drug in foreign markets

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

/s/

Andrei Nabakowski
5/6/04 11 10 08 AM
CSO
NDA 21-361/Rifaximin
This is the PSC memo which was circulated and agreed upon

Renata Albrecht
5/12/04 04 00 09 PM
MEDICAL OFFICER

Mark Avigan
5/13/04 05 37 40 PM
DRUG SAFETY OFFICE REVIEWER

14 Page(s) Withheld

3

_____ Page(s) Withheld

CONSULTATION RESPONSE
Division Of Medication Errors And Technical Support
Office Of Drug Safety
(DMETS, HFD-420)

Date Received	**Desired Completion Date**	**ODS CONSULT#** 04-0116
April 26, 2004	May 15, 2004 **PDUFA Date** May 26, 2004	

TO

Renata Albrecht
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH

Andrei Nabakowski
Project Manager, Division of Special Pathogen and Immunologic Drug Products
HFD-590

PRODUCT NAME	**NDA SPONSOR**
Xifaxan (Rifaximin) Tablets 200 mg **NDA#** 21-361	Salix Pharmaceuticals, Inc

SAFETY EVALUATOR Alina R Mahmud, R Ph

RECOMMENDATIONS

1 DMETS has no objections to the use of the proprietary name Xifaxan We consider this a final review If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward

2 DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review

3 DDMAC finds the proprietary name Xifaxan acceptable from a promotional perspective

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone 301-827-3242 Fax 301-443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420, Parklawn Rm 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW April 28, 2004

NDA NUMBER 21-361

NAME OF DRUG Xifaxan
(Rifaximin Tablets)
200 mg

NDA SPONSOR Salix Pharmaceuticals, Inc

I INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), to review the proprietary name, Xifaxan™, regarding potential name confusion with other proprietary and established drug names Blister and container labels as well as insert and patient labeling were submitted for review and comment

This is the seventh proprietary name review for this application On March 18 2002, the proprietary names 'Lumenax' and — ODS Consult 01-0226) were submitted by the sponsor and found unacceptable by DMETS In a second review dated September 24, 2002, (ODS Consult 01-0226-1), the proprietary names, — and — were found unacceptable by DMETS In a third review dated August 20, 2003, (ODS Consult 03-0185), the proprietary names — was found unacceptable but DMETS had no objections to the alternate name, — However, subsequently on November 24, 2003, the sponsor notified the Agency that due to an editorial error at the time of submission, the tradename — , was submitted instead of the intended trademarked trade name, — In a review dated March 1, 2004 DMETS reviewed the proprietary name — and found it unacceptable (see ODS consult 03-0320)

PRODUCT INFORMATION

Xifaxan tablets are indicated for the treatment of patients (12 years-old or older) with traveler's diarrhea caused by E coli — For traveler s diarrhea, the recommended dose is one 200 mg tablet three times a day for three days Xifaxan can be taken with or without food Xifaxan tablets are available in bottles of 30 tablets

II RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Xifaxan to a degree where potential confusion between drug names could occur under the usual clinical practice settings A search of the electronic online version of the U S Patent and Trademark Office's Text and Image Database[4] was also conducted The Saegis Pharma-In-Use database[5] was searched for drug names with potential for confusion An expert panel discussion was conducted to review all findings from the searches In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name

A EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Xifaxan Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing Advertising and Communications (DDMAC) The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name

1 DDMAC finds the proprietary name, Xifaxan, acceptable from a promotional perspective

2 The Expert Panel identified three proprietary names as having the potential for confusion with Xifaxan Additionally, the currently marketed drug product Biaxin was identified as having a potential for confusion from the prescription studies conducted by DMETS See Table 1 (page 4) for dosage forms available and usual dosage

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name dosage form(s) strength	Usual adult dose*	Other**
Xifaxan	Rifaximin Tablets, 200 mg	One tablet three times a day for three days	N/A
Xalatan	Latanoprost Ophthalmic Solution 0 005%	Instill 1 drop in affected eye(s) once daily in the evening	L/A
Cefoxitin (established name)	Cefoxitin Powder for Injection 1g 2 g 10 g (vials and infusion bottles)	1 to 2 g every 6 to 8 hours	L/A

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX Inc 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740 which includes all products/databases within ChemKnowledge, DrugKnowledge and RegsKnowledge Systems

[2] Facts and Comparisons, online version, Facts and Comparisons, St Louis, MO

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book

[4] WWW location http /www uspto gov/tmdb/index html

5 Data provided by Thomson & Thomson s SAEGIS ™ Online Service available at www thomson thomson com

Ciloxan	Ciprofloxacin Ophthalmic Solution 3 5 mg/mL Ointment 3 33 mg/g	*Corneal Ulcers* 2 drops into the affected eye every 15 minutes for the first 6 hours and then 2 drops into the affected eye every 30 minutes for the remainder of the first day On the 2nd day, instill two drops in the affected eye hourly On the 3rd through the 14th day, place two drops in the affected eye every four hours Treatment may be continued after 14 days if corneal re-epithelialization has not occurred *Bacterial Conjunctivitis* 1-2 drops instilled into the conjunctival sac(s) every 2 hours while awake for two days and 1-2 drops every four hours while awake for the next five days	L/A
Biaxin	Clarithromycin Tablets 250 mg 500 mg Oral Suspension 125 mg/5 mL	1 tablet twice daily for 7 to 14 days	S/A
*Frequently used, not all-inclusive **L/A (look-alike) S/A (sound-alike)			

B PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text Likewise, an orthographic algorithm exists which operates in a similar fashion The POCA identified five additional names which were considered to have significant orthographic and/or phonetic similarity to Xifaxan

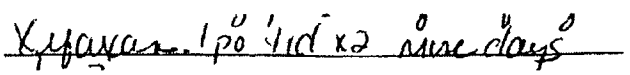
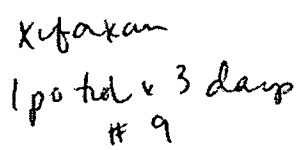
Table 2 Potential Sound-Alike/Look-Alike Names Identified by POCA

Product Name	Established name dosage form(s) strength	Usual adult dose*	Other**
Xifaxan	Rifaximin Tablets 200 mg	One tablet three times a day for three days	N/A
Betoxon	Levobetaxolol Ophthalmic Suspension 0 5%	No longer marketed	L/A
Cytoxan	Cyclophosphamide Tablets 25 mg 50 mg Lyophilized Powder for Injection 100 mg	1 to 5 mg/kg/day for initial and maintenance dosing	L/A
Robaxin	Methocarbamol Tablets 500 mg 750 mg Injection 100 mg/mL	Tablets 1 5 g four times daily Injection 3 g for three consecutive days	L/A
Rifadin	Rifampin Capsules 150 mg 300 mg Powder for Injection 600 mg	600 mg once daily	L/A
Mefoxin	Cefoxitin Powder for Injection 1g 2 g 10 g (vials and infusion bottles)	1 to 2 g every 6 to 8 hours	L/A

C PRESCRIPTION ANALYSIS STUDIES

1 Methodology

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Xifaxan with marketed U S drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses) This exercise was conducted in an attempt to simulate the prescription ordering process An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Xifaxan These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail In addition, the outpatient orders were recorded on voice mail The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient Rx sample 	Xifaxan, give one tablet three times daily for 3 days Dispense 9 tablets
Outpatient Rx sample 	

2 Results

Three study participants from the verbal prescription studies provided the interpretation Bifaxan while one participant interpreted the proposed name as Bifaxa These interpretations are similar to the currently marketed drug product Biaxin See appendix A for the complete listing of interpretations from the verbal and written studies

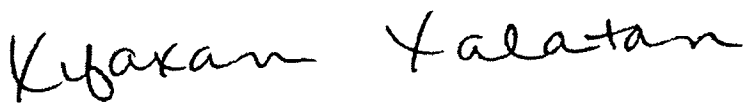
D SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Xifaxan, the Expert Panel identified the drug names, Xalatan, Ciloxan, and Cefoxitin The POCA identified the drug names Mefoxin, Betoxin, Cytoxin, Robaxin, and Rifadin The drug product Biaxin was identified as having a potential for confusion with Xifaxan as a result of four interpretations provided in the verbal prescription study conducted by DMETS Of these aforementioned names, Mefoxin and Cefoxitin will be reviewed simultaneously since Cefoxitin is the established name for the proprietary name Mefoxin Additonally, Betoxin will not be reviewed further since it is no longer available in the U S marketplace and it does not appear in the 2003 Red Book or on-line or printed references such as Facts and Comparisons, Physician's Drug Reference and the Orange Book Betoxin and Xifaxan also differ in dosage form, route of administration, dosing regimen and indication for use

DMETS conducted prescription studies to simulate the prescription ordering process In this case, there was no confirmation that Xifaxan could be confused with any of the aforementioned names However, three study participants from the verbal prescription studies provided the interpretation Bifaxan while one participant interpreted the proposed name as Bifaxa These interpretations are similar to the currently marketed drug product Biaxin The majority of the remaining misinterpretations were misspelled/phonetic variations of the proposed name, Xifaxan

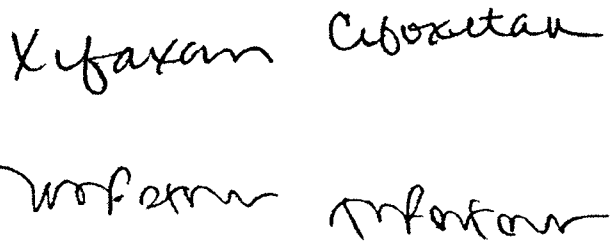
1 Look-alike Name Confusions

a Xalatan may look similar to Xifaxan when scripted Xalatan contains latanoprost and is indicated for reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension Xalatan and Xifaxan begin with the letter "X" and end with the letters "an" Additionally, the middle letters in each name "alat" vs "ifax" may also appear similar when scripted (see writing sample below) However, the down stroke of the letter "f" in Xifaxan helps to differentiate the product names The drug products differ in dosage form, route of administration, dosing regimen, and duration of use (chronic vs 3 days) Although it is possible for a prescription for either drug product to be written with the directions "Use as directed", a prescription for Xifaxan will most likely reference the dosing instructions "three times daily for 3 days" Despite orthographic similarities between the names, the likelihood for confusion is minimal given the differences in product characteristics



b Cefoxitin and Mefoxin may look similar to Xifaxan when scripted Cefoxitin is the established name for Mefoxin and is indicated for the management of infections caused by susceptible gram-positive cocci and gram-negative rods The letters "efox" vs "ifax" may look similar when scripted as do the ending letters "in" vs "an" in Cefoxitin and Xifaxan, respectively The first letter "X" in Xifaxan differs in script from the first letter "C" in Cefoxitin Additionally, Cefoxitin contains the additional letters "it" which contributes to their name differences (see page 7) Mefoxin and Xifaxan share the similarly scripted

letters "efoxin" vs "ifaxan" However, the names begin with different letters (M vs X) The drug products Mefoxin (cefoxitin) and Xifaxan differ in dosage form, route of administration, strength, and indication for use Although the products share an overlapping dosing regimen (every 8 hours vs three times daily), the differences in names (Cefoxitin vs Xifaxan and Mefoxin vs Xifaxan) and product characteristics help to distinguish one product from the other



c Ciloxan and Xifaxan may look similar when scripted Ciloxan contains Ciprofloxacin and is indicated for the treatment of superficial ocular infections involving the conjunctiva or cornea due to strains of microorganisms susceptible to antibiotics The ending letters (oxan vs axan) can look similar (see below) However, the names are distinguishable due to differences in the first letter "C" vs "X" and the down stroke of the letter "f" in Xifaxan which Ciloxan does not contain (see below) The drug products differ in dosage form, route of administration, and dosing regimen Although a prescription for either drug product may be written without a strength, the lack of convincing look-alike potential and the differences in product characteristics should minimize the likelihood for confusion

d Cytoxan and Xifaxan were found to have look-alike potential Cytoxan contains cyclophosphamide which is indicated as an antineoplastic The ending letters "oxan" vs "axan" may look similar when scripted If the down stroke of letter "y" in Cytoxan is scripted in close proximity with the letter "t", this combination may resemble the letters "if" in Xifaxan (see below) However, the names differ in the first letter "C" vs "X" The products share an overlapping dosage form and route of administration Cytoxan and Xifaxan differ in strength (tablets 25 mg, 50 mg, injection 100 mg vs 200 mg), dose, dosing regimen, indication for use, and prescriber population Given these differences the likelihood for confusion is minimal

e Robaxin and Xifaxan have the potential to look similar Robaxin contains methocarbamol and is indicated for use as a skeletal muscle relaxant The first letter of each name "R" vs "X" looks somewhat similar as do the endings "baxin" vs "faxan", especially since the scripted letter "b" in Robaxin looks almost identical the letter "f" in Xifaxan (see page 8) The drug products share an overlapping dosage form and route of administration However, the products

differ in strength, dose, and dosing regimen Despite similarities in name, the likelihood for confusion is minimal given the differences in product characteristics

Rifadin Xifaxan

f Rifadin and Xifaxan were identified as having the potential to look similar Rifadin contains rifampin and is indicated for the treatment of tuberculosis The first letter in each name may look similar (R vs X) as do the endings "in" vs "an" Additionally each name contains the letters "ifa" in the middle However the "d" in Rifadin vs the "x" in Xifaxan look somewhat different (see below) The drug products share an overlapping dosage form and route of administration The products differ in strength, dose, dosing regimen, and duration of use (chronic vs acute) A prescription for Xifaxan will most likely specify the directions "1 tablet three times daily for 3 days" This will help differentiate Rifadin from Xifaxan Despite similarities in name, the likelihood for confusion is minimal given the differences in product characteristics

Rifadin Xifaxan

g Biaxin and Xifaxan have the potential to sound similar Biaxin contains clarithromycin and is indicated for the treatment of mild to moderate infections caused by susceptible strains of designated microorganisms The names Biaxin and Xifaxan share a rhyming quality as they are comprised of three syllables, share a long "i" sound, and the similarly pronounced ending "xin" vs "xan" However, the "f" in Xifaxan helps in distinguishing it from Biaxin This was apparent in the prescription studies as all participants included the letter "f" in their interpretation Biaxin and Xifaxan share similar dosage form and route of administration However, they differ in strength (250 mg, 500 mg, 125 mg/5 mL vs 200 mg) and dosing regimen Additionally, Xifaxan will most likely be written with the instructions "1 tablet three times daily for 3 days" whereas a prescription for Biaxin will be written for a duration of use of 7 to 10 days Despite similarities in the names, the potential for confusion between Biaxin and Xifaxan is minimal

III LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the draft blister and container labels as well as the draft insert and patient labeling of Xifaxan, DMETS has focused on safety issues relating to possible medication errors, and has identified the following areas of possible improvement, which might minimize potential user error

A — LABEL

B CONTAINER LABEL

IV RECOMMENDATIONS

A DMETS has no objections to the use of the proprietary name Xifaxan We consider this a final review If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling must be re-evaluated A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward

B DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review

C DDMAC finds the proprietary name, Xifaxan, acceptable from a promotional perspective

DMETS would appreciate feedback of the final outcome of this consult We would be willing to meet with the Division for further discussion, if needed If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-2102

Alina R Mahmud, R Ph Date
Team Leader
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Appendix A

Voice	Inpatient	Outpatient
Bifaxa	Xefaxan	Xifaxam
Bifaxin	Xefaxan	Xifaxam
Bifaxin	Xefaxan	Xifaxam
Bifaxin	Xefaxan	xifaxan
Ditensin	Xefaxan	Xifaxan
Lisaxin	Xefaxan	Xifaxan
Lyfaxin	Xifaxan	Xifaxan
Sifaxin	Xifaxan	Xifaxan
Vifaxin	Xifaxan	Xifaxan
Viphaxin	Xifaxan	Xifaxan
Visaxin	Xifaxan	Xifaxan
Visaxin	Xifaxan	Xifaxan
Zifaxin	Zifaxar	Xifaxan
Zyfaxin		Xifaxan
Zyfaxin		Xifaxan
Zyfaxin		Xifaxan
		Xitaxan

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

---

/s/

Alina Mahmud
5/7/04 02 32 57 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/7/04 03 32 01 PM
DRUG SAFETY OFFICE REVIEWER

46 Page(s) Withheld

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS, HFD-400)

DATE RECEIVED 10-11-2001	**DUE DATE** 5-6-2002	**ODS CONSULT #** 01-0226

TO Renata Albrect, MD
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH Diana Willard, Project Manager
HFD-590

PRODUCT NAME	**SPONSOR** Salix Pharmaceuticals, Inc
Lumenax (Primary) — (Alternate) (Rifaximin Tablets) 200 mg **NDA #** 21-361	

SAFETY EVALUATOR Marci Ann Lee, PharmD

SUMMARY In response to a consult from the Division of Special Pathogen and Immunologic Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of proposed proprietary names "Lumenax" and — to determine the potential for confusion with approved proprietary and established names as well as pending names

DMETS RECOMMENDATION DMETS does not recommend the use of the proprietary names "Lumenax" or — DMETS recommends implementation of the labeling and packaging revisions described in Section III Please forward copies of the final printed labels and labeling when they are available

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
one (301) 827-3242 Fax (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration