

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-554

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022554

SUPPL #

HFD # 180

Trade Name XIFAXAN Tablets

Generic Name rifaximin

Applicant Name Salix Pharmaceuticals, Inc.

Approval Date, If Known March 24, 2010

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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

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

Type 6 NDA

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 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.

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:

d) Did the applicant request exclusivity?

YES NO

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

7 Years

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

YES NO

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

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

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

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

NDA# 021361

XIFAXAN (rifaximin) Tablets 200 mg

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

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 NDAs 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

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"):

RFHE3001: A Multi-Center, Randomized, Double-Blind, Placbeo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerability of Rifaximin 550 MG BID for 6 Months in Preventing Hepatic Encephalopathy

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 # 59133 YES ! NO
! Explain:

RFHE3001: A Multi-Center, Randomized, Double-Blind, Placbeo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerability of Rifaximin 550 MG BID for 6 Months in Preventing Hepatic Encephalopathy

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?

Not applicable to this application

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:

Name of person completing form: Hee (Sheila) Lianos

Confidential
Title: Project Manager
Date: March 18, 2010

Page 8

3/24/2010

Name of Office/Division Director signing form: Joyce Korvick, MD
Title: Acting Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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

/s/

HEE K LIANOS
03/24/2010

JOYCE A KORVICK
03/24/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22554 Supplement Number: _____ NDA Supplement Type (e.g. SE5):
Type 6 NDA

Division Name: Division of Gastroenterology PDUFA Goal Date: March Stamp Date: 6/24/2010
Products 24, 2010

Proprietary Name: Xifaxan Tablets

Established/Generic Name: Rifaximin

Dosage Form: Tablets

Applicant/Sponsor: Salix Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) treatment of patients (> 12 years of age) with Travelers' Diarrhea caused by noninvasive strains of Escherichia coli.

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Reduction in risk of overt hepatic encephalopathy (HE) in patients with liver disease.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 Disease/condition does not exist in children
 Too few children with disease/condition to study
 Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22554

ORIG-1

SALIX
PHARMACEUTICA
LS INC

XIFAXAN

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/s/

HEE K LIANOS
03/24/2010

1.3.3. Debarment Certification

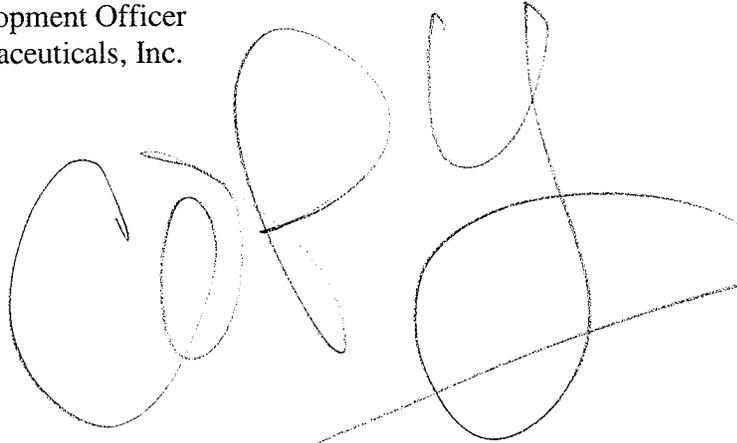
Salix Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act in connection with this application to NDA 21-361/S-010.



William P. Forbes, Pharm.D.
Senior Vice President, Research and Development and
Chief Development Officer
Salix Pharmaceuticals, Inc.

June 23, 2007

Date





NDA 022554

LABELING COMMENTS

Salix Pharmaceuticals
Attention: Gail Glifort, RAC
Senior Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your new drug application (NDA) dated and received on June 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xifaxan (rifaximin) 550 mg Tablets.

We have reviewed your proposed package insert for Xifaxan and are providing you with our comments to facilitate labeling negotiations (see Attachment 1). We request that you review our proposed revisions and submit a response to NDA 022554 by March 15, 2010.

If you have any questions please call me at (301) 796-4147.

Sincerely yours,

{See appended electronic signature page}

Hee (Sheila) K. Lianos, RPh., PharmD.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment: (1) Xifaxan Package Insert with FDA Comments (redline)
(2) Xifaxan Package Insert with FDA Comments (clean)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22554

ORIG-1

SALIX
PHARMACEUTICA
LS INC

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/s/

HEE K LIANOS
03/12/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022554

PDUFA GOAL DATE EXTENSION

Salix Pharmaceuticals, Inc.
Attention: Gail Glifort, RAC
Sr. Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your June 24, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xifaxan (rifaximin) 550mg Tablets.

On October 13, 2009, we received your October 12, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 24, 2009.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-4147.

Sincerely yours,

(See appended electronic signature page)

Matthew Scherer, MBA
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22554

ORIG-1

SALIX
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LS INC

XIFAXAN

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/s/

MATTHEW C SCHERER
10/29/2009



NDA 022554

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: David Dobrowski
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Dobrowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xifaxan® (rifaximin) 550 mg Tablets.

We are reviewing your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please provide a response by close of business on Friday, October 9, 2009.

1. For the RFHE3001 study, please provide results for the following responder analyses. Each responder analysis result should present patient counts for responses and failures (per responder definitions below) by treatment group while also conducting an appropriate statistical test for association (e.g., Fisher's Exact Test).
 - a. You may use the following responder definitions (one definition per responder analysis):
 - i. A responder is a patient who does not experience a breakthrough HE episode throughout the entire 6 month study.
 - ii. A responder is a patient who does not experience a breakthrough HE episode for at least 5 months after first dose of study drug.
 - iii. A responder is a patient who does not experience a breakthrough HE episode for at least 4 months after first dose of study drug.
 - iv. A responder is a patient who does not experience a breakthrough HE episode for at least 3 months after first dose of study drug.
 - v. A responder is a patient who does not experience a breakthrough HE episode for at least 2 months after first dose of study drug.
 - vi. A responder is a patient who does not experience a breakthrough HE episode for at least 1 month after first dose of study drug.
 - b. Per responder definition in the first bullet under 1(a)(i), given above, please further subcategorize and present the patient counts for failures by:

- i. Whether the breakthrough-HE episode resulted in any hospitalization (and the duration of this hospitalization) or not.
- ii. The duration of breakthrough-HE episode.
- iii. Whether the breakthrough-HE episode occurred as a consequence of any precipitating complications (sepsis, any GI bleeding, ascites, SBP, etc.) or not.
- iv. Whether the breakthrough-HE episode was diagnosed by a physician or a caregiver.

Each of these failure counts should be presented by treatment group. No statistical testing is required.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-4147.

Sincerely,

(See appended electronic signature page.)

Brian Strongin, RPh., MBA
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

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Product Name

NDA-22554

ORIG-1

SALIX
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/s/

BRIAN K STRONGIN
10/02/2009



NDA 022554

FILING COMMUNICATION

Salix Pharmaceuticals, Inc.
Attention: David Dobrowski
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Dobrowski:

Please refer to your new drug application (NDA) dated June 24, 2009, received June 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xifaxan (rifaximin) 550 mg Tablets.

We also refer to your submission(s) dated, July 28, 2009, August 4, 2009, August 7, 2009, and August 11, 2009, which contained study data from your paper submission in electronic format.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. There is only one pivotal Phase 3 clinical trial. In general, it has been the FDA's position that at least two adequate and well-controlled studies are needed to establish effectiveness. (*See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998).
2. Your primary endpoint was the time to first breakthrough overt hepatic encephalopathy (HE) episode; as defined as an increase of Conn score to Grade ≥ 2 (i.e., 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. The clinical meaningfulness of your definition (of a breakthrough overt HE episode) is unknown.

Clinical pharmacology

3. The effect of severe hepatic impairment on PK and safety is unknown. The effect of mild to moderate hepatic impairment on PK was evaluated in patients with a history of HE. It was noted that in your Phase 3 trial most patients had a Model for End-Stage Liver Disease (MELD) score of 11-18 which corresponds to moderate hepatic impairment and none had a MELD score greater than 18. The area under the curve (AUC) of rifaximin in patients with moderate hepatic impairment was 50% or 58% greater than in patients with mild hepatic impairment based on Child-Pugh Classification and MELD score, respectively.

Nonetheless, there is no information for effect of severe hepatic impairment on PK of rifaximin as well as on safety and efficacy. A subgroup analysis for safety based on a varying degree of hepatic impairment would be helpful yet the lack of information should be adequately reflected in the label.

4. Induction of CYP3A4 by rifaximin was observed based on decreased midazolam AUC by ~25%. As higher systemic exposure is expected in a majority of the target patient population, your label should have appropriate language about CYP3A4 induction potential of rifaximin.
5. There was no TQT study conducted.

Statistics

6. A Per-Protocol (PP) population definition was not included in the RFHE3001 SAP and thus should be clearly defined. Subsequently, all primary analysis tables and figures should be repeated with this PP population to show the robustness of the primary efficacy data.
7. Two further sensitivity analyses should be conducted for the primary efficacy endpoint in the RFHE3001 study. First, along with subjects who discontinued due to experiencing a breakthrough HE, all other subjects that discontinued due to any other reason prior to the completion of the six month treatment period should also be categorized as if they experienced a breakthrough HE treatment failure at that discontinuation time point. Second, along with subjects who discontinued due to experiencing a breakthrough HE, all other subjects that discontinued due to adverse events (AE), liver transplant, or death prior to the completion of the six month treatment period should also be categorized as if they experienced a breakthrough HE (i.e., failure) at that discontinuation time point.
8. For the RFHE3001 study, please provide all screening data (electronic) on every patient who failed screening and subsequently did not participate in the trial.
9. For the RFHE3001 study, please provide the SAS programs corresponding to all efficacy outputs presented (all section 14.2 tables and figures).
10. There were peculiar issues/anomalies in the RFHE3001 data sets which imply that the clinical (and subsequently analysis) database may not be 100% clean. Examples include missing randomization numbers in the RAND domain (214 out of 299 patients had missing randomization numbers), and some patients in the AE analysis data set show more adverse events than what they show in the corresponding AE raw data set. These issues/anomalies should be explained and corrected.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-4147.

Sincerely,

{See appended electronic signature page}

Brian Strongin, RPh., MBA
Chief Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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/s/

BRIAN K STRONGIN
09/03/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022554

PRIORITY REVIEW DESIGNATION

Salix Pharmaceuticals, Inc.
Attention: David Dobrowski
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Dobrowski:

Please refer to your new drug application (NDA) dated and received on June 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xifaxan (rifaximin) 550 mg Tablets.

We also refer to your submission(s) dated, July 28, 2009, August 4, 2009, August 7, 2009, and August 11, 2009, which contained study data from your paper submission in electronic format.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 24, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 24, 2009.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 6, 2009.

If you have any questions, call Hee (Sheila) Lianos, Regulatory Project Manager, at (301) 796-4147.

Sincerely,

(See appended electronic signature page)

Cristi Stark, M.S.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

CRISTI L STARK
08/24/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022554

NDA ACKNOWLEDGMENT

Salix Pharmaceuticals
Attention: Gail Glifort, RAC
Senior Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xifaxan (rifaximin) 550 mg Tablets

Date of Application: June 24, 2009

Date of Receipt: June 24, 2009

Our Reference Number: NDA 022554

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 23, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you

submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions please contact me at (301) 796-4147.

Sincerely,

{See appended electronic signature page}

Hee (Sheila) Lianos, RPh., PharmD
Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Hee K Lianos
7/23/2009 10:44:22 AM

Cristi Stark
7/23/2009 10:46:04 AM



IND 59, 133

Salix Pharmaceuticals, Inc.
ATTENTION: Gail Glifort, RAC
Senior Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rifaximin Tablets.

We also refer to the meeting between representatives of Salix and the FDA on December 16, 2008. The purpose of this meeting was to discuss the rationale for using Rifaximin as treatment of Hepatic Encephalopathy (HE) and the status of your clinical development program (including the Phase 3 clinical study recently completed) in preparation for a future New Drug Application (NDA) submission.

At this meeting, FDA agreed to provide you with more detailed answers to Questions 3, 4, 5, and 7 of your December 16th meeting background materials received on November 7, 2008. Below find your questions followed by our responses in bold:

3. The proposed safety database will contain the following safety pools:
 - a. The primary safety pool will contain 335 unique subjects who received Rifaximin in the HE population (RFHE3001 and RFHE3002) and analyzed per the Statistical Analysis Plan (SAP).
 - b. Three secondary safety pools will contain data from populations treated for: Treatment of HE (RIF/HE/INT/99, RFHE9702 and RFHE9701); Treatment of Travelers' Diarrhea (RFID9601, RFID9701, RFID 9801, RFID3001) and; Prevention of Travelers' Diarrhea (RFID3003, RFID3004, RFID3005, RFID3006, RFID2001). The secondary safety pools will include analyses of patient exposure, demographics, common adverse events, and discontinuations due to an adverse event (AE) as detailed in the SAP.
 - c. Additionally, Phase 2 studies in other indications and Phase 1 studies will be individually summarized.

Q. Does the Agency concur with the proposed safety pools and proposed statistical analysis plan (SAP)? (See Attachment 2)

FDA Response:

The current proposals appear adequate. The final acceptability regarding safety pools, efficacy, and statistical analysis plan will be a review issue.

4. Salix intends to include an Integrated Summary of Safety (ISS) in Module 5.3.5.3 and a Summary of Safety in Module 2.7.4. Salix also proposes to provide narratives for subjects from RFHE3001 and RFHE3002 who died, had a serious adverse event (SAE), discontinued due to an AE, or who had a breakthrough HE episode.

Q. Does the Agency concur with the proposed presentation of safety data and narrative criteria for the NDA?

FDA Response:

The approach appears adequate however, any determination of final adequacy will be addressed once your NDA submission has been reviewed and evaluated.

5. The Phase 3 study (RFHE3001) along with the controlled clinical trials conducted in active HE (RFX/HE/INT/99, RFHE9702, RFHE9701) as well as published studies with use of Rifaximin in hepatic encephalopathy will form the basis of evidence for efficacy. Salix is proposing to include a Summary of Efficacy in Module 2.7.3 which will include study RFHE3001, reviews of the literature, and the supportive HE studies. Therefore, a full Integrated Summary of Efficacy (ISE) will not be included in Module 5.

Q. Does the Agency concur with the proposed presentation of efficacy data?

FDA Response:

Submissions with incomplete information in Module 5 may result in filing issues. Please submit the ISE in module 5 (see the Agency's "*Guidance for Industry: M4E: The CTD Efficacy.*")

Note: you currently plan to submit a single Phase 3 study (RFHE3001) along with PK/PD data (e.g. from study RFHE9702) to support an NDA approval. We generally recommend two Phase 3 studies to support an NDA approval. You must decide whether or not to risk submitting the data you currently have versus including data from an additional Phase 3 study.

7. Salix proposes to cross-reference the microbiology section of the NDA to the approved NDA (NDA 21-361) as well as summarize important published literature or unpublished data available to Salix since 2000.

Q. Does the Agency concur with the proposed presentation of microbiology data?

FDA Response:

It is acceptable to cross-reference an approved NDA and summarize published literature. It remains unclear why you only want to submit only data since the year 2000 and not include any data from before the year 2000. We would like to see the pre-2000 data that is available as part of your review submission.

We also make reference to your January 22, 2009, telephone conversation with Dr. Sheila Lianos, Regulatory Project Manager from our division, requesting changes and corrections to the meeting minutes for the December 16, 2008 meeting. You requested the addition of two participants: Mark McDougal, Clinical Project Manager [REDACTED] (b) (4)

[REDACTED] as their names were omitted in the list of participants. Also, you have requested the deletion on page 4 of the [REDACTED] (b) (4) (another GI company) name and substitution with your company name. FDA agrees with these changes and this letter will be incorporated in the official IND files to corroborate our agreement with the changes you have requested.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Marlène G. Swider, Regulatory Project Manager, at (301) 796-2104.

Sincerely,

{See appended electronic signature page}

Donna J. Griebel, M.D.
Director,
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name / Subject

IND 59133

SALIX
PHARMACEUTICALS
INC

RIFAXIMIN TABLETS

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

/s/

DONNA J GRIEBEL
04/03/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 59,133

Salix Pharmaceuticals, Inc.
Attention: Gail Glifort, RAC
Senior Manager, Regulatory
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rifaximin Tablets.

We also refer to the meeting between representatives of Salix and the FDA on December 16, 2008. The purpose of this meeting was to discuss the rationale for using Rifaximin as treatment of Hepatic Encephalopathy (HE) and the status of your clinical development program (including the Phase 3 clinical study recently completed) in preparation for a future New Drug Application (NDA) submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4146.

Sincerely,

{See appended electronic signature page}

Hee (Sheila) K. Lianos, RPh., PharmD.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 16, 2008
TIME: 1:30 – 2:30 p.m., EST
LOCATION: White Oak Campus, Silver Spring, MD 20903
Bldg 22, room 1417
APPLICATION: IND 59,133
DRUG NAME: Rifaximin Tablets
TYPE OF MEETING: Type B (Pre-NDA)

MEETING CHAIR: Hugo Gallo-Torres, MD, PhD, PMS

MEETING RECORDER: Hee (Sheila) K. Lianos, PharmD.

FDA ATTENDEES: (Title and Office/Division)

Division of Gastroenterology Products, ODE III:

Hugo Gallo-Torres, MD, PhD, PMS	Medical Team Leader
Virginia Elgin, MD	Medical Officer
Anil Nayyar, MD	Medical Officer
Donna Griebel, MD	Division Director
Ruyi He, MD	(Acting) Deputy Division Director
Insook Kim, PhD	Clinical Pharmacology Reviewer
Mike Welch, PhD	Biostatistics Team Leader
Behrang Vali	Biostatistics Reviewer
David Joseph, PhD	Nonclinical Pharmacology Team Leader
Yuk-Chow Ng, PhD	Nonclinical Pharmacology Reviewer
Hee (Sheila) Lianos, PharmD	Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Representing Salix Pharmaceuticals:

Bill Forbes, MD	Vice President, R & D and Chief Development Officer
Enoch Bortey, PhD	Executive Director, Biostatistics, Data Management and Programming
David Dobrowski	Director, Regulatory Affairs
Audry Shaw, PhD	Director, Clinical Development
Kumal Merchant, PhD	Manager, Clinical Development
Shirley Huang, MS	Senior Biostatistician, Biostatistics
Gail Glifort	Senior Manager, Regulatory Affairs
Lisa Hampton	Regulatory Specialist

BACKGROUND:

On October 18, 1999, the original Investigational New Drug (IND) Application was submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the use of Xifaxan (rifaximin) Tablets for the indication of Hepatic Encephalopathy (HE).

Since the original submission, Salix Pharmaceuticals has held two other meetings with the FDA in regard to their application for IND 59,133:

On December 13, 2004, Salix Pharmaceuticals met with the FDA in a Type C meeting to discuss the Phase 3 development plan for Rifaximin Tablets, including protocol RFHE3001, "A Multi-Center, Randomized, Double Blind, Placebo-Controlled Trial to Compare the Effectiveness, Safety and Tolerability of Rifaximin 400mg BID as Compared to Placebo During 8 Weeks of Dosing" as well as the collection of pharmacokinetic (PK) data in a sub-study of patients enrolled in a long-term safety study, RFHE3002.

On November 14, 2007, Salix Pharmaceuticals held a teleconference with the FDA in a Type C meeting to discuss the Agency's concerns regarding Study RFHE3002 which were raised during the December 13, 2004, industry meeting. Specifically, the PK sub-study was discussed.

On October 6, 2008 (received October 7, 2008), Salix Pharmaceuticals requested and was granted a Type B (Pre-NDA) meeting with the Agency to discuss their Phase 3 study results for the use of Rifaximin for the maintenance of remission from HE. Meeting background materials were received by Salix on November 7, 2008.

ADDITIONAL REGULATORY INFORMATION (cross-referenced applications):

The following have been cross-referenced by Salix Pharmaceuticals in their October 6, 2008, submission:

(b) (4)
[Redacted]
NDA 21-361
[Redacted] (b) (4)

MEETING OBJECTIVES:

The purpose of the December 16, 2008, meeting was to discuss the rationale for using Rifaximin as treatment of Hepatic Encephalopathy (HE) and the status of the development program (including the Phase 3 clinical study recently completed) as proposed by Salix Pharmaceuticals in preparation for a future New Drug Application (NDA) submission.

DISCUSSION POINTS:

Following introductions, Salix's questions, from the November 6, 2008, background information package, were used as the basis for further discussion regarding their clinical study and other supportive data (as submitted).

The format of these minutes provides for Movetis' questions (and pre-meeting responses) in regular typeface, followed by the Agency's responses in **bolded** print, followed by the December 16, 2008, meeting discussion in *italic and bolded* print.

QUESTIONS (as stated in Salix's November 6, 2008, background package), RESPONSES AND ADDITIONAL DISCUSSION:

Prior to discussion between Salix and the FDA, Salix conducted a brief presentation, "Hepatic Encephalopathy: A Significant Complication of Cirrhosis" by (b) (4). The slides from (b) (4) presentation are enclosed as an appendix following these meeting minutes

9.1 Medical/Statistical

1. Hepatic encephalopathy (HE) is a serious clinical condition which is typically reversible. The maintenance of remission in patients with a history of HE is a serious and unmet clinical need that has no currently approved drug therapy. Salix has recently completed a Phase 3 study (RFHE3001) in which data show a compelling effect in the maintenance of remission in patients with HE. Salix believes that the data are in accordance with the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), in that the "trial demonstrated a clinically meaningful effect on the prevention of a disease with [a] potentially serious outcome." In addition to the data from the RFHE3001, there are several supportive clinical trials conducted, over 20 clinical trials published in the literature as well as multiple published meta-analyses that support the utility of Rifaximin in patients with HE. Does the Agency concur that, in accordance with the FDA guidance, the available efficacy information constitutes sufficient evidence of efficacy for an NDA submission and substantive review for the orphan indication of the maintenance of remission in patients with HE?

Agency Preliminary Response:

No, we do not concur. Based on the information in your background package we do not consider the efficacy results to be robust. We have the following concerns and comments:

- **The clinical significance of your primary endpoint is not clear.**

Salix provided the following response, in writing prior to the meeting, as clarification:

The primary endpoint was agreed upon during the December 2004 (Type C) meeting, as defined by an increase in Conn Score to Grade ≥ 2 or a concurrent increase in both Conn Score and Asterixis grade by 1 each from baseline (see attached meeting minutes). In addition, this endpoint has been discussed at great length with the hepatology community that is responsible for the care of patients with HE. The overwhelming consensus has supported the primary endpoint of this study as appropriate and important. In most patients at risk, HE occurs as an episodic deterioration in mental status that may result in hospitalization. It is

important to note that 56% of all patients reaching the primary endpoint as defined above were hospitalized for this reason.

We regret that the clinical importance of our data was not clear to the Division. We hope to clarify these data by presentation in greater detail at our meeting.

Additional Discussion:

The Agency encouraged Salix to provide data that clearly supports the clinical significance of their endpoints (i.e., reproducible in a second study, and or tracking of the Asterixis scoring)

- **We have serious concerns about your methodology for assessing both your primary and secondary endpoints.**

Salix provided the following response, in writing prior to the meeting, as clarification:

We believe that the methods used for assessment of primary and secondary endpoints represent the most valid and widely accepted methods used in this field. The methodology assessing the endpoints was detailed in the draft protocol discussed during the Type C meeting (December 2004) about which the Division's comments were incorporated in the development of the primary endpoint. We hope that Salix's responses to the other points raised in the Division's response will clarify the validity of our methodology definitively. From the Division's response Salix is unsure of the specific concerns regarding methodology in this study.

- **The Conn Score result differences between the two treatment arms are not clinically significant.**

Salix provided the following response, in writing prior to the meeting, as clarification:

The pertinent Conn Score results for this study are those that developed transiently at the time of HE breakthrough, ie, at the time the primary endpoint was reached. This difference in the Conn Scores between the 2 treatment arms was highly significant both statistically and clinically. (See table below.) Confusion may have arisen from our additional presentation of Conn Score data collected throughout the study at routine visits and at EOS visits when patients were commonly in remission and, therefore, had Conn Scores reflective of their baseline status.

Breakthrough HE Criteria	Placebo	Rifaximin	Total	p value*
	N=159	N=140	N= 299	RFX vs PBO
	n (%)	n (%)	n (%)	

Overall Breakthrough HE	73 (45.9)	31 (22.1)	104 (34.8)	0.000019
Conn \geq 2 (Baseline score 0 or 1)	56 (35.2)	28 (20.0)	84 (28.1)	0.004
Concurrent increase in both Conn and Asterixis of 1 each from baseline (Baseline score= 0)	17 (10.7)	3 (2.1)	20 (6.7)	0.004

*p value reflects the Fisher's Exact Test.

Additional Discussion:

The Agency stated that the data supporting Salix's methodology will be a review issue at the time of NDA submission.

- **There is clinically significantly higher daily lactulose use in the treatment arm compared to placebo which may have confounded efficacy results.**

Salix provided the following response, in writing prior to the meeting, as clarification:

The nominal difference between the daily mean doses was heavily influenced by two subjects in the rifaximin group who consumed very large amounts of lactulose throughout their participation in the study (average daily dose 93 and 90 cups; 1 cup = 15 mL). Both subjects were in fact treatment failures (Day 19 and 12, respectively) thus tending to diminish the apparent effectiveness of rifaximin. If these 2 outliers are excluded from the analyses the average daily lactulose use (4.12 and 4.17 cups per day for placebo and rifaximin, respectively) is virtually indistinguishable between the two treatment arms. This is also evident from the median daily lactulose use shown in Table 14.1.6.a which is 3.00 versus 2.99 cups per day for placebo and rifaximin, respectively. It is important to note that the average daily use of lactulose by subjects completing 6 months treatment was equal in both the placebo and rifaximin groups (3.17 versus 3.16 cups per day, respectively). Therefore, lactulose use did not influence the study outcome.

In addition, as noted by the Division at our Type C meeting in December 2004, the efficacy of lactulose for HE prevention has not been rigorously demonstrated and, as a result the agent has not been approved by the FDA for this purpose. The Division's comments in December 2004 were in keeping with the meta-analysis published by Als-Nielsen et al. (BMJ, 2004). Based on information from published literature, Salix believes a clinically meaningful dose of lactulose has not been identified.

- **Please clarify the duration of the breakthrough HE episodes.**

Salix provided the following response, in writing prior to the meeting, as clarification:

As discussed with the Division during the Type C meeting, there was no intention to assess data on the duration of each episode of HE breakthrough. Per the Type C discussion, this study was designed to measure the impact of rifaximin on the frequency of, and the time to, HE events. The duration of HE events is not an applicable measure of HE remission.

You should conduct another well controlled study. Please submit your new protocol for review prior to conducting this study. Please justify the primary efficacy endpoints and provide evidence of the validity of the instruments you propose to use.

Salix provided the following response, in writing prior to the meeting, as clarification:

Salix does not believe another clinical study is required to establish the efficacy and safety of rifaximin treatment to maintain remission in patients with HE. The previously agreed upon primary endpoint is both highly statistically significant and clinically meaningful. The robustness of the data is corroborated by the subgroup analyses. We intend to discuss this further with you at our meeting.

RFHE3001 is one of the largest and most comprehensive, prospective evaluations of an effective therapy for HE, a serious, unmet medical condition. Salix believes that the data are in accordance with the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998), in that a single, adequate and well-controlled study can be used to “demonstrate a clinically meaningful effect on the prevention of a disease with [a] potentially serious outcome.” Additionally, consistent with the Guidance and as discussed in the Type C meeting, the results of RFHE3001 with other pertinent information from other rifaximin studies including other doses, other stages of disease, in other populations, and different endpoints, support the results of the single, adequately well-controlled study demonstrating effectiveness of rifaximin in HE.

Additional Discussion:

(Slide, “Hepatic Encephalopathy: A Significant Complication of Cirrhosis” by Dr. A. Sanyal was presented. This slide will follow the meeting minutes)

2. Salix is proposing to submit an NDA in the 1st quarter of 2009 for the maintenance of remission in patients with HE. At the time of initial NDA filing the primary safety database will include approximately 127 exposures for less than 6 months, 208 exposures for 6 – 12 months and, 57 exposures for at least 12 months. Salix is proposing to supplement the primary safety database in the 120-Day Safety Update and anticipates exposures of 61 for less than 6 months, 274 for 6 – 12 months and, 160 for at least one year. Does the Agency concur that this plan provides adequate safety data to ensure a substantive review of the NDA?

Agency Preliminary Response:

No, we do not concur. Please refer to the International Conference on Harmonization (ICH) Safety guidelines. NDA safety data should be complete at the time of submission. See our response to question 1.

Salix provided the following response, in writing prior to the meeting, as clarification:

Rifaximin was first approved in Italy in 1985 and is currently approved in 24 countries for multiple indications including HE. Rifaximin was approved and marketed in the US since May 2004. The proposed safety database contains substantial data regarding safety in patients treated with rifaximin for HE as well as other indications. The safety database will include approximately 2,200 unique patients treated with rifaximin in clinical studies. Salix intends to discuss the available data at the meeting and justify our request to utilize these data as outlined above.

3. The proposed safety database will contain the following safety pools:
 - a. The primary safety pool will contain 335 unique subjects who received Rifaximin in the HE population (RFHE3001 and RFHE3002) and analyzed per the SAP.
 - b. Three secondary safety pools will contain data from populations treated for: Treatment of HE (RIF/HE/INT/99, RFHE9702 and RFHE9701); Treatment of Travelers' Diarrhea (RFID9601, RFID9701, RFID 9801, RFID3001) and; Prevention of Travelers' Diarrhea (RFID3003, RFID3004, RFID3005, RFID3006, RFID2001). The secondary safety pools will include analyses of patient exposure, demographics, common adverse events, and discontinuations due to AE as detailed in the SAP.
 - c. Additionally, Phase 2 studies in other indications and Phase 1 studies will be individually summarized.

Does the Agency concur with the proposed safety pools and proposed statistical analysis plan (SAP)? (See Attachment 2)

Agency Preliminary Response:

Please refer to our response to questions 1 and 2.

4. Salix intends to include an Integrated Summary of Safety (ISS) in Module 5.3.5.3 and a Summary of Safety in Module 2.7.4. Salix also proposes to provide narratives for subjects from RFHE3001 and RFHE3002 who died, had a serious adverse event (SAE), discontinued due to an adverse event (AE), or who had a breakthrough HE episode. Does the Agency concur with the proposed presentation of safety data and narrative criteria for the NDA?

Agency Preliminary Response:

It would be premature to respond to this question at this time. Please refer to our responses to questions 1 and 2.

5. The Phase 3 study (RFHE3001) along with the controlled clinical trials conducted in active HE (RFX/HE/INT/99, RFHE9702, RFHE9701) as well as published studies with use of Rifaximin in hepatic encephalopathy will form the basis of evidence for efficacy. Salix is proposing to include a Summary of Efficacy in Module 2.7.3 which will include study RFHE3001, reviews of the literature, and the supportive HE studies. Therefore, a full Integrated Summary of Efficacy (ISE) will not be included in Module 5. Does the Agency concur with the proposed presentation of efficacy data?

Agency Preliminary Response:

Please refer to our response to questions 1 and 2.

6. Salix is proposing the following indication: Rifaximin is indicated for the maintenance of remission in patients with hepatic encephalopathy. Does the agency concur with this proposed indication statement?

Agency Preliminary Response:

It would be premature to respond at this time. The indication is based on the population studied in the pivotal trials.

Salix provided the following response, in writing prior to the meeting, as clarification:

Salix believes that study RFHE3001 was appropriately designed and demonstrated efficacy and safety in patients with HE. Therefore the totality for the proposed NDA is sufficient to support the indication of maintenance of remission in patients with hepatic encephalopathy.

7. Salix proposes to cross-reference the microbiology section of the NDA to the approved NDA (NDA 21-361) as well as summarize important published literature or unpublished data available to Salix since 2000. Does the Agency concur with the proposed presentation of microbiology data?

Agency Preliminary Response:

Based on the data provided, we would not recommend that you submit an NDA at this time.

8. Based on the results of embryo-fetal toxicity studies submitted in the original NDA (21-361), Rifaximin was labeled with a Pregnancy Category C designation. ^{(b) (4)}



Agency Preliminary Response:

We will re-evaluate the current (b) (4) for Rifaximin based on your submitted new analysis of data from (b) (4). Until the report of the reanalyzed data has been thoroughly evaluated, the Division is unable to comment on the sufficiency of the new report (b) (4).

9.2 Clinical Pharmacology / Biopharmaceutics

1. Salix has completed or is performing additional pharmacokinetic (PK) studies based on discussions with the Agency at an End-of Phase 2 meeting in December 2004 and a PK teleconference call in November 2007, e.g., HE patient PK and in vitro P-gp substrate/inhibition studies. Salix has also conducted a PK study with healthy volunteers in a fasted/fed state and at the proposed dose (550 mg BID). Salix believes that these new studies along with the studies included in the original NDA (NDA 21-361) complete the PK profile for Rifaximin. Does the Agency concur that Salix has fulfilled our PK obligations as previously discussed for the HE indication?

Agency Preliminary Response:

It appears that you have multiple dose PK, food effect, drug interaction studies with midazolam and PK in HE patients using 550 mg tablets. We also note that in vitro P-gp transporter studies are on-going and your preliminary results indicate that Rifaximin may be a substrate of P-gp transporter. Depending on your in vitro studies, an in vivo drug interaction study with a likely co-administered P-gp inhibitor may be warranted. PK studies conducted using different dosage regimens from the proposed dosage regimen may or may not be applicable to the new NDA. In your submission, please clarify the difference or sameness of formulations for different strengths.

We have the following comments for a future NDA submission:

- We request that you include the in vitro study reports using human materials (e.g., the in vitro transporter studies and cytochrome P450 studies) in the clinical pharmacology section when the NDA is submitted. Please, provide the RFHE9702 dose-finding study report for review as well.
- We noted that you plan to cross-reference some study reports to NDA 21-361. It will be helpful, for review purposes, if full study reports of the most relevant studies (e.g., the mass balance study) were submitted to the new NDA. In particular, please submit the full reports of bioanalytical assay validation along with in-run QC reports.
- We noted that the mean AUC of Rifaximin in HE patients with moderate hepatic impairment was about 36% higher than in HE patients with mild hepatic impairment. Please provide safety analysis via subgroup analysis as you define the subgroups with HE who have varying degrees of liver

impairment. Please, include PK data where possible in these subgroup analyses.

9.3 Nonclinical

1. Study 1310-001, a two-year rat oral carcinogenicity study and Study 1310-009, a 26-week study in transgenic mice conducted with Rifaximin have recently completed testing and are undergoing analyses. Salix believes, in accordance with the ICH Guidance for Industry: M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (July 1997), that carcinogenicity testing may be concluded post approval for this indication to treat a serious disease. Does the Agency agree that these studies may be submitted post approval?

Agency Preliminary Response:

We concur that hepatic encephalopathy is a serious disease currently without approved therapy for treatment. Although we agree that according to the ICH M3 guidance, carcinogenicity studies may be submitted post approval for the proposed indication (i.e., maintenance of remission of hepatic encephalopathy), we recommend that you submit the carcinogenicity study reports as soon as possible.

2. Salix is proposing to include a nonclinical summary in Module 2.6 summarizing all studies completed for Rifaximin. Studies previously submitted and reviewed as part of NDA 21-361 for traveler's diarrhea will be cross referenced within the Module 2 summary but not resubmitted in the HE NDA. All studies completed since approval of NDA 21-361 will be provided as part of the HE NDA submission and included in Module 4 as well as summarized in Module 2.6. Does the Agency concur with this presentation of the non-clinical data?

Agency Preliminary Response:

We concur that you are not required to submit the nonclinical studies that have been reviewed under NDA 21-361. All studies completed since approval of NDA 21-361 should be included in a future NDA submission.

9.4 Regulatory

1. Salix is planning on submitting a paper NDA in CTD format. A draft table of contents (TOC) is provided in the meeting package. Does the agency concur that a paper NDA in CTD format is acceptable and that the TOC is sufficient to allow a thorough and complete review of the NDA? (See Attachment 4)

Agency Preliminary Response:

Currently, a paper NDA in CTD format is acceptable. However, we prefer that an electronic version accompany the paper version as it will facilitate a more timely review.

2. Rifaximin for the use in hepatic encephalopathy has been granted orphan drug designation. As stated in the Pediatric Research Equity Act, "Unless the Secretary

requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526.” Therefore, Salix does not believe it necessary to request a pediatric waiver in the NDA. Does the Agency concur that Salix is exempt from requesting a pediatric waiver for this indication?

Agency Preliminary Response:

Salix is exempt from requesting a pediatric waiver if the Rifaximin has been granted orphan status. Orphan status does not trigger PREA. Note: if you plan to label your product for use in the pediatric population you have to do at least one pediatric study. The label would reflect the results of a pediatric study or studies, whether positive, neutral, or negative.

3. Salix has been granted an orphan designation (2017-07-16001) for hepatic encephalopathy. Because HE is a serious condition associated with liver failure for which there is no approved therapy, Salix is requesting a priority review of the NDA. Does the Agency concur that a priority review of the application is warranted?

Agency Preliminary Response:

Priority versus standard review is determined at the time of filing. The final decision will be sent to you in writing at the time of filing.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 59133

SALIX
PHARMACEUTICALS
INC

RIFAXIMIN TABLETS

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

/s/

HEE K LIANOS
01/16/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,133

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
Regulatory Affairs Consultant
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Mr. Kashiwase:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xifaxan (rifaximin) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2004. The purpose of the meeting was to discuss the clinical development plan for Xifaxan Tablets for the orphan indication of hepatic encephalopathy.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9333.

Sincerely,

[See appended electronic signature page]

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Memorandum of Meeting Minutes

Meeting Date: December 13, 2004
Meeting Time: 11:00-12:30 p.m.
Meeting Location: Potomac Conference Room, 3rd Floor Parklawn

Application Number: IND 59,133
Drug Name: Rifaximin
Type of Meeting: Type C
Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D.
Meeting Recorder: Monika Houstoun, Pharm.D.

BETWEEN:

Salix Pharmaceuticals, Inc.

Lorin Johnson, PhD, Chief Scientist
David Taylor, MD, Chief Medical Officer
Robert Haake, PhD, Executive Director, Biostatistics
Tawana Wester, RN, Associate Director, Clinical Development
Janice McKellar, MA, Associate Director, Regulatory Affairs
Nathan Bass, MD, Consultant/ Hepatic Encephalopathy Clinical Consultant
James M. Hinson Jr., MD, Consultant/Clinical Development
David Kashiwase, Consultant/Regulatory Affairs

AND

Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180

Joyce Korvick, M.D., M.P.H., Acting Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Gail Moreschi, M.D., Medical Officer
Sushanta Chakder, Ph.D., Pharmacology Reviewer
David Joseph, Ph.D., Pharmacology Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)

Stella Grosser, Ph.D., Statistical Team Leader

Office of Orphan Products Development, HF-035

Donald Haggerty, M.D., M.P.H., Medical Officer

PURPOSE:

To discuss the clinical development plan for Xifaxan (rifaximin) Tablets for the indication of hepatic encephalopathy.

BACKGROUND:

On February 10, 1998, Rifaximin, under the tradename of (b) (4) received Orphan Drug Designation for the treatment of hepatic encephalopathy.

On October 14, 1999, a Salix Pharmaceuticals, Inc. submitted an IND for Xifaxan (rifaximin) Tablets for the treatment of hepatic encephalopathy.

On October 27, 2004, Salix Pharmaceuticals, Inc. submitted a meeting request for a meeting to discuss clinical development plan for Xifaxan (rifaximin) Tablets. On November 12, 2004, Salix submitted a background package containing nonclinical information and questions.

Responses to the questions posed by the sponsor were faxed to the sponsor on December 8, 2004.

DISCUSSION:

Responses to the questions posed by the sponsor.

IND 59,133
Specific questions for the Agency

The following are draft questions for the Medical Reviewer.

1. The hepatic encephalopathy patient population consists of those with minimal hepatic encephalopathy, episodic (acute) hepatic encephalopathy, or those in remission of hepatic encephalopathy. Clinical data from 19 studies in which patients in an acute episode of hepatic encephalopathy were treated with rifaximin are available. Can the Division provide input concerning the use of a meta-analysis of these data to support an episodic (acute) hepatic encephalopathy indication?

FDA Response:

Clinical data from 19 studies is important for safety. However, to prove that a compound is effective, a meta-analysis is not usually considered adequate.

This information may be supportive of an indication in a future submission with additional clinical data.

2. With respect to the Phase 3 study design for a maintenance of remission indication:
 - a. Comparator Controls

- i. Placebo Comparator

1. Salix is proposing a (b) (4)
Does the Division have any comments with respect to this proposed study design?

FDA Response:

This would be an acceptable study design.

- ii. Active Comparator

1. In the event that during further protocol development it is determined that for a specified hepatic encephalopathy patient population an active control comparator is necessary Salix is proposing to use (b) (4) study design. Does the Division agree that the active comparator and the (b) (4) study design are acceptable?

FDA Response:

(b) (4) would be an acceptable active comparator. As an alternative, you might consider neomycin. However, a (b) (4) study design is not appropriate as neither (b) (4) nor neomycin is approved for this indication. Therefore, regardless of the "active comparator" you elect to use, the study design would have to be of superiority.

2. With respect to the (b) (4) active control comparator (b) (4) study design, can the Division provide guidance concerning an acceptable sample size?

FDA Response:

Please see our answer to 2.a.ii.1 above.

3. Due to the unique nature of (b) (4) Salix may consider conducting the study as a (b) (4) study (i.e., (b) (4) Does the Division agree with this approach?

FDA Response:

Although, an open-label approach might be appropriate, such a study design is often inadequate to minimize bias. A double-dummy design is preferable. It should

be noted that the some literature reports suggest (b) (4) is not different from the placebo.

- b. For the propose placebo controlled Phase 3 study, does the Division agree with the Inclusion criteria?

FDA Response:

The inclusion criteria are acceptable.

- c. For the propose placebo controlled Phase 3 study, does the Division agree with the use of mental status as the Primary Endpoint?

FDA Response:

The Mental Status should be included but also consider an asterixis evaluation.

(b) (4)

This is acceptable.

- d. For the propose placebo controlled Phase 3 study, Does the Division agree with the sample size of the placebo controlled study?

FDA Response:

It is acceptable.

- e. For the propose placebo controlled Phase 3 study, does the Division agree with the rifaximin dose and duration of treatment?

FDA Response:

Your approach seems acceptable.

- f. Does the Division have any additional comments concerning the general proposed placebo study design?

FDA Response:

No. Please see our answer to question 4 below.

3. For an Orphan Drug product, at the time of submission, can the Division provide input concerning expected size of the Safety Database?

FDA Response:

Refer to the ICH guidelines. The Orphan Drug Act does not provide any exemption from approval criteria.

At the time of the Orphan Drug designation was granted, the target population for this indication was at approximately (b) (4)

This can be further discussed at the Pre-NDA meeting, it was agreed that both 6 month and 12 month exposure data will be needed.

4. Salix acknowledges that for Orphan Drug products two adequate and well-controlled studies may be necessary. Does the Division agree that for a hepatic encephalopathy indication only a single adequate and well-controlled study is necessary?

FDA Response:

Although usually 2 adequate and well controlled studies are necessary, a single large study which is well designed and well executed may suffice. Please refer to the Guidance for Industry on Clinical Effectiveness.

5. Does the Division agree that the proposed Phase 3 protocol would be appropriate for a Special Protocol Assessment review?

FDA Response:

Possibly yes. However, this would be decided when the protocol is submitted and is determined, among other things, that the submission is complete. Please refer to the Guidance for Industry: Special Protocol Assessment.

Additional Comments:

With inpatient use of this antibiotic, could cross-resistance to rifampin develop, specifically regarding tuberculosis?

Sponsor will address this issue.

Rifampin, a structurally-related drug, has been reported to induce intestinal P-glycoprotein as well as other drug transporting proteins (e.g. MRP2) in humans (Greiner et al., J Clin Invest, 104(2), pg. 147-153, 1999 & Fromm et al., Am J Pathol, 157(5), pg. 1575-1580, 2000). A 26-week oral toxicity study in rats demonstrated a marked reduction in systemic drug concentrations at termination, which is

suggestive of drug interactions as a substrate and inducer for P-glycoprotein or other transporters. Please comment.

Sponsor is collecting additional PK data in patients enrolled in long-term safety studies. After evaluating that data we will discuss the need for additional drug-drug interaction studies.

CONCLUSIONS:

- The use of a meta-analysis of clinical data from 19 studies in which patients in an acute episode of hepatic encephalopathy were treated with rifaximin may be supportive of an indication in a future submission with additional clinical data.
- The sponsor has proposed a rewording of the primary endpoint, as follows: “The primary (b) (4)

- The size of the Safety Database can be further discussed at the Pre-NDA meeting, it was agreed that both 6 month and 12 month exposure data will be needed.
- Sponsor will address the issue of possible cross-resistance to rifampin developing, specifically regarding tuberculosis, with inpatient use.
- Sponsor is collecting additional PK data in patients enrolled in long-term safety studies. After evaluating that data we will discuss the need for additional drug-drug interaction studies.

Minutes Preparer: _____
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Chair Concurrence: _____
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