PtID	Treatment group (Placebo, Rifax 600 mg/day, Cipro)	MITT (Y/N)	Evaluable (Y/N)	Pretreatment pathogen (Species)	Day isolated relative to treatmt start	Pretreatment MIC (μg/ml)		Posttreatment MIC (μg/ml)		Clinical Outcome		Micro Outcome	Days on study drug	TL US (hr)	Center	Study (#)
						Rifax	Cipro	Rifax	Cipro	Well ness	Treatm ent failure					
X1*				ETEC												
X1*				*Salmonella* species												
X1*				*C jejuni*												
X2				*Shigella flexneri*												
X3				*Shigella sonnei*												

*Underlined patients with mixed infection at baseline
TLUS Time to last unformed stool

Please contact me at (301) 827-2127 if you have any questions regarding this facsimile transmission

Andrei E Nabakowski, Pharm D Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Andrei Nabakowski
1/14/04 09 54 00 AM
NDA 21-361/Rifaximin micro table request

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE November 5, 2002

To	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin

Total no of pages including cover 3

Regarding NDA 21-361/rifaximin tablets, the Division has the following comments

1 The DMF for was reviewed and found deficient The DMF holder, has been notified Please inform the agency after the DMF holder has submitted their response to the deficiencies

2 Please submit validation reports for the drug product assay, related substances and the dissolution methods as agreed upon by the firm with the FDA inspector during the establishment inspection of facility by the agency

3 There is considerable variation in the f_2 values when the dissolution profiles of batches F0982 001, C2F0051, C2F0052, and C2F0053 are compared with that of the clinical lot 99002 Please explain these variations

4 You have proposed the following dissolution method and specification for the release and stability testing of the rifaximin drug product

Dosage Form	Tablets
Strength	200 mg rifaximin
Apparatus Type	
Medium	
Medium Volume	
~ Speed	
Sampling Time	
Temperature	
Dissolution Specification	Q = ~ at ~

Based on the data submitted, the Division recommends the following **interim** dissolution method and specification

Dosage Form	Tablets
Strength	200 mg rifaximin
Apparatus Type	~
Medium	
Medium Volume	
~ Speed	
Sampling Time	
Temperature	
Dissolution Specification	Q = ~ at ~

Please utilize the above interim dissolution method and specification proposed by the Division to collect dissolution data from both the stability batches and the commercial lots used in the rifaximin clinical trials Individual commercial lot tablets should be used for collection of these data The data collected using this interim dissolution method and specification will be analyzed to set a final dissolution specification

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---

Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
11/5/02 12 17 40 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE November 4, 2002

To	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject IND 52,980/rifaximin Please see the attached comments from our reviewers regarding your September 24, 2002 submission to IND 52,980

Total no of pages including cover 6

Regarding your September 24, 2002 submission to IND 52,980/rifaximin tablets, our reviewers have the following comments

Clinical Comments

1 We recommend that all subjects have blood cultures (minimum of 2) at screening Those subjects with positive cultures should be withdrawn and treated with conventional antimicrobials Subjects withdrawn due to clinical worsening or failure should have two blood cultures obtained prior to the institution of other antimicrobial treatment We would like to remind you that these subjects should be considered treatment failures

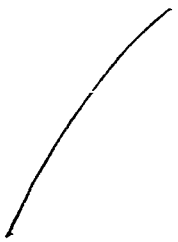
2 We recommend that a full physical exam, including orthostatic measurements, be performed at screening Subjects with evidence of orthostatic hypotension (a

decrease of systolic blood pressure greater than 10 mm Hg or increase in heart rate of > 20 beats per minute) should be excluded from the study

3 Please perform a complete serum chemistry evaluation including serum blood urea nitrogen, serum creatinine, and ALT, AST, T Bili (plus fractionated bilirubin if elevated), and alkaline phosphatase at screening and at the end-of-treatment/follow-up visit If abnormalities develop, the patient should be followed, appropriate medical evaluation performed and the abnormal tests should be followed until normalization occurs The details of any such events should be fully reported in your submission

4 Please explain why all subjects who receive ANY antimicrobial within 7 days are not excluded

5



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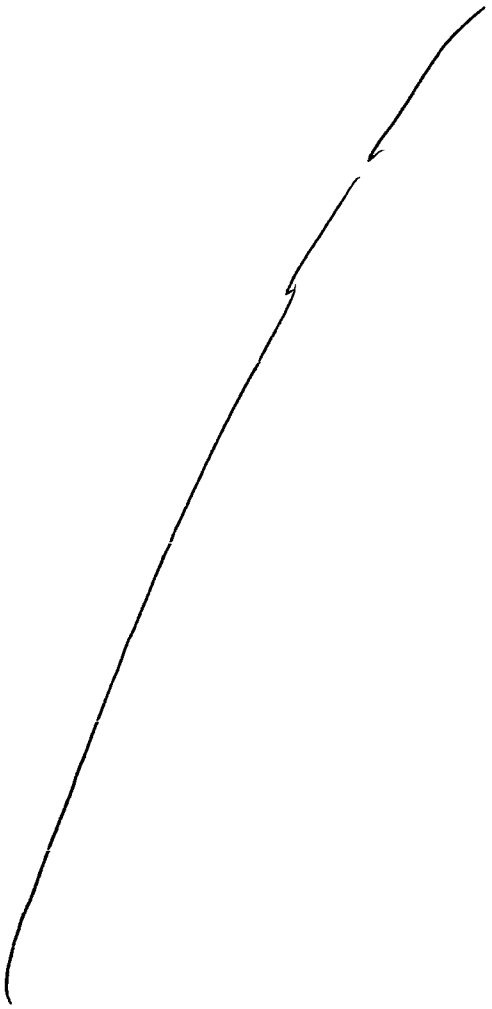


10 Based upon what is described in your protocol, your study will be performed in patients hospitalized in Mexico and Peru Please record the country of citizenship for persons enrolled in the study You should also be prepared to discuss how the data from this study apply to the U S population and U S medical practice

Statistical Comments

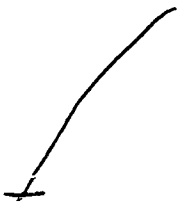
11 Based on placebo-controlled studies, we believe that a non-inferiority limit of 0 5 for the hazard ratio is too small For this more serious indication and the lack of systemic coverage of rifaximin, a limit of 0 6 is more appropriate

12 Please note that we perform all one-sided tests at a significance level of 0 025

Microbiological Comments

13 Please identify all pathogens to the species level

14



Biopharmaceutics Comments

15 We recommend that you evaluate the extent of systemic absorption of rifaximin after oral administration in dysenteric patients When you have developed a plan to address this request, we recommend that you submit your proposal for the Division's review

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Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
11/4/02 12 44 35 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE November 4, 2002

To —	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number —	**Fax Number** 301-827-2475
Phone Number —	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin/tradename

Total no of pages including cover 6

Regarding your July 22, 2002 submission to NDA 21-361/rifaximin tablets, the Division of Medication Errors and Technical Support (DMETS) has the following comments

DMETS does not recommend use of the proprietary name, — However, at this time DMETS has no objections to the use of the proprietary name, —

These recommendations are based on the reasons described below

Risk Assessment for —

3 Page(s) Withheld

F INSERT LABELING

No comments at this time

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Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Diana Willard
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Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE November 1, 2002

To —	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number —	**Fax Number** 301-827-2475
Phone Number —	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin

Total no of pages including cover 3

Regarding your September 16, 2002 submission to NDA 21-361/rifaximin tablets, our reviewers have the following comments

1 Your proposal to substitute the safety data from the 104 hepatic encephalopathy (HE) patients from study RFHE9701 (data included in the original safety database) with patient safety data from study Rif/HE/INT/99, for your primary safety population, is acceptable (because of the concerns that have been identified regarding the integrity of the data from study RFHE9701) However, the safety data from these 104 patients from study RFHE9701, as well as the results of the audit, should be included in your submission The safety data from the 104 patients should be presented separately, but in a similar fashion to the primary safety data

2 The data from RFHE9702 should not be excluded from your primary safety population UNLESS the ongoing audit of this study finds a problem that calls the integrity of these data into question Should such a problem be identified in the

future, we should have further discussions regarding how the data from RFHE9702 should be handled

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Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
11/1/02 10 43 27 AM
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FACSIMILE TRANSMITTAL SHEET

DATE June 20, 2002

To —	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number —	**Fax Number** 301-827-2475
Phone Number —	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin

Total no of pages including cover 5

Our chemist has the following comments/requests regarding NDA 21-361

1 We note that the — commercial drug substance lots and — per year thereafter will be subject to complete release testing (Amendment of May 9, 2002) Please describe the analytical methods that are to be used Please also consider performing an assay on each lot of drug substance that is received

2 We note that the drug product analytical methods were validated by — — (see Vol 4, pp 191 – 196) and not by the drug product manufacturer — (see their method description at Vol 4, pp 148 – 156, which does not contain any validation details) Please provide data to show that the methods were validated at —

3 The tablets will be packaged in — — HDPE bottles Please confirm that all four configurations will be marketed commercially Please also provide data to show that the — for each container-closure system are similar

4 We are unable to accept the three batches manufactured by Alfa Wasserman as primary stability batches Q1A(R) states that "stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing" However, the Alfa Wasserman batches are packaged in ——— ——— Also, the — materials used at Alfa Wasserman are not identical to those used at — and the — packaging equipment is not described The batch sizes at Alfa Wasserman (— ablets) are considerably less than the proposed commercial batch size (— tablets) So that we may make a decision concerning the expiry date please send any updated stability data concerning batches made at the commercial site, — Please also supply data for individual impurities/degradants

5 Please commit to placing the first three commercial batches on stability at 40°C/75% RH as recommended by Q1A(R) (section 2 2 4)

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Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
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FACSIMILE TRANSMITTAL SHEET

DATE June 6, 2002

To —	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number /	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin/June 3, 2002 submission

Total no of pages including cover 3

We have the following comments regarding your June 3, 2002 submission to NDA 21-361

1 Your proposal for the numbers of tablets from each lot to be used for dissolution, assay, and content uniformity testing is acceptable

2 Please clarify which Lot Numbers of Plenolyt and Baycip were used in Study N2404 In the report for Study N2404, submitted to the original NDA, you identify the Baycip lot as N-1 and the Plenolyt lot as N-7 (see page 25/700) In your submission of 6/3/02, you identify the Plenolyt Lot as N-1 and the Baycip lot as N-7

3 Please generate full dissolution profiles for all tablets in all media to be tested We recommend, for comparison, that you use the sampling times that were used in Study N4006

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Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Diana Willard
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Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE June 4, 2002

To —	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number —	**Fax Number** 301-827-2475
Phone Number —	**Phone Number** 301-827-2485

Subject NDA 21-361/rifaximin/trade name

Total no of pages including cover 5

The Division of Medication Errors and Technical Support (DMETS) does not recommend use of the proposed proprietary names Lumenax or — This recommendation is based on the reasons described below

Risk Assessment for LUMENAX

Lovenox has potential for look-alike and sound-alike confusion with Lumenax These names begin and end with the same letters and contain the same number of syllables and letters, which increases the likelihood for confusion When handwritten, "LOVE-" can look similar to "LUME-" as does "-NOX" and "-NAX " Lovenox is used to treat a different condition than Lumenax and it is an injectable medication, unlike Lumenax Although the dosage strengths for Lovenox do not overlap with Lumenax, it would be possible to use two 100 mg/1 mL prefilled syringes to equal the 200 mg dose of Lumenax, in error Both Lumenax and Lovenox can be used for a short course of therapy Lovenox is used in a different type of patient population and is typically

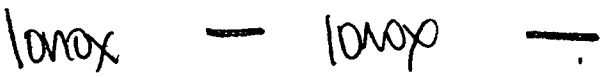
prescribed by a different type of specialist than Lumenax It is possible that Lovenox and Lumenax will be stored near each other in some pharmacies

Zovirax has potential for look-alike confusion with Lumenax Zovirax is available as a 200 mg oral capsule, similar to Lumenax Both medications are used to treat infections and require a short course of treatment Lumenax and Zovirax could be prescribed by the same type of specialist Although the dosing schedule for Zovirax is different from Lumenax, both medications are administered multiple times daily

Risk Assessment for —

Luvox has potential for look-alike and sound-alike confusion Luvox and — start and end with the same letters, share the same number of syllables and have the same number of letters, which contributes to their look-alike and sound-alike similarity Although there is no overlap in the dosage strengths, it would be possible to use two 100 mg Luvox tablets to equal a 200 mg dose of — Luvox is used to treat a different condition and is used on a more chronic basis, unlike — Luvox has a different dosing schedule and is prescribed by a different type of specialist However, Luvox and — could be stored near one another on a pharmacy shelf Although there are many different factors, the names are very similar and confusion is likely

Lonox has look-alike and sound-alike similarity to — Lonox and — start and end with the same letters, share the same number of syllables and have the same number of letters, which contributes to their look-alike and sound-alike similarity Additionally, the letters "a," "o," and "u" can look similar when handwritten, as do "m" and "n " Lonox is a combination product that is used to treat a different condition thar — Although Lonox is administered on a different dosing schedule thai — they are both dosed multiple times daily — and Lonox could be stored near each other on the pharmacy shelf, increasing the likelihood for confusion



Xanax has look-alike similarity to — which is based mostly on the ending letter combinations of "-anax" and — Xanax is available in different dosage strengths and used to treat a different condition than — However, both medications are administered on a three times daily dosing schedule Although Xanax and — are both available as oral solid dosage forms, it is unlikely that they would be stored near each other

Xanax — [illegible] start —, po tid

Eurax looks similar to — when handwritten The letters "e" and "l" can be confused Additionally, "-urax" and ' — look the same However, Eurax is available as a topical cream or lotion unlike — Eurax is used for a short course of therapy to treat scabies infestations Comparatively — is used for a short course of therapy to treat infections of the gastrointestinal tract, including traveler's diarrhea Eurax is administered on a different schedule than — Eurax and — are not likely to be stored near one another in a pharmacy Although there are some differences between the products, these names are very similar and confusion is likely

lumax — urax —

Draft container label, draft carton labeling, insert labeling, and patient information leaflet

In addition, DMETS has reviewed the draft container label, draft carton labeling, insert labeling, and patient information leaflet for Lumenax — and has attempted to focus on safety issues relating to possible medication errors Areas of possible improvement in the interest of minimizing potential user error have been identified

A GENERAL COMMENT

It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used on the marketplace (i e , color, placement of name, etc) Please forward copies of the final printed labels and labeling when they are available

B — CONTAINER LABEL

1

1 Page(s) Withheld

F INSERT LABELING

1 Clarify the HOW SUPPLIED section for the — packaging configuration

2 Clarify the meaning of "Product of (to be determined) "

Recommendations

A DMETS does not recommend the use of the proprietary name "Lumenax "

B DMETS does not recommend the use of the proprietary name ' —

C DMETS recommends implementation of the labeling and packaging revisions described above Please forward copies of the final printed labels and labeling when they are available

Please contact me at (301) 827-2485 if you have any questions regarding this facsimile transmission

Diana M Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Diana Willard
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FACSIMILE TRANSMITTAL SHEET

DATE May 20, 2002

To	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number	**Fax Number** 301-827-2475
Phone Numbe	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 3

We have the following requests from our Clinical Pharmacology & Biopharmaceutics reviewer regarding your NDA 21-361

1) Please conduct dissolution testing to compare the lots of Plenolyt used in Study RFID9701 (Lot L-05) and Study N2404 (Lot N-7) Testing should be as conducted in Study N4006, using the same three media and conditions

2) Please conduct dissolution testing to compare the lots of Baycip used in Study N2404 (Lot N-1) and Study N4006 (Lot P114) Testing should be as conducted in Study N4006, using the same three media and conditions

3) Please indicate if each lot of Plenolyt and Baycip used in the above studies meets the specifications for Ciprofloxacin Tablets in the United States Pharmacopeia with respect to dissolution, assayed potency, and content uniformity of dosage units

Please contact me at (301) 827-2485 if you have any questions regarding the above requests

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
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Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE May 3, 2002

To	**From** Diana M Willard
Company	Division of Special Pathogen and Immunologic Drug Products
Fax Number	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 2

We have the following request regarding NDA 21-361

> We notice (e g , section 3 1 3 2 2) that the drug product will be manufactured, packaged, and labeled at the — plants at —— —— Can you confirm that tablet manufacture, packaging, and labeling will take place at each plant or will the responsibilities be divided between the plants?

Please contact me at (301) 827-2485 if you have any questions regarding the above comments

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
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CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE March 27, 2002

To /	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number /	**Fax Number** 301-827-2475
Phone Number /	**Phone Number** 301-827-2485

Subject IND 52,980/rifaximin tablets

Total no of pages including cover 4

Please refer to your February 1, 2002 submission to IND 52,980 for rifaximin, serial number 058 We have the following requests/comments regarding the proposed protocol for Study RFID3001 included in this submission

1 Please note that the review of your NDA 21-361 for Lumenax™ Tablets is on-going Based upon our review to date, the clinical microbiologic efficacy data from study RFID9801, in general, do not appear to distinguish the antimicrobial activity of rifaximin from that of placebo Therefore, we recommend that the protocol for proposed Study RFID3001 be modified in order to provide the data needed to adequately assess both clinical and microbiological efficacy For example, you might consider performing daily stool cultures on each patient in order to examine antimicrobial effects over time as a means of demonstrating microbiological efficacy In addition, we encourage you to gather information from the medical literature on the natural history of traveler's diarrhea and the time course for stool cultures to revert to negative for the pathogens under study in the presence antimicrobial therapy and in absence of antimicrobial therapy We look forward to reviewing your proposal

to address this issue

It will also be important to examine the correlation between clinical outcome by baseline pathogen and clinical microbiologic efficacy by baseline pathogen on a per patient basis This analysis will be of particular interest because of the possibility that the clinical microbiologic efficacy assessment may be made during a time when the patient is receiving antimicrobial therapy

2 Please ensure that all pathogens are speciated

3 It would be useful to have a listing with Patient ID, Pathogen Pre-treatment, Pathogen Post-treatment, MIC for Rifaximin, MIC for Ciprofloxacin, and Clinical Outcome There should be one chart for each treatment group, i e , rifaximin, ciprofloxacin, and placebo

4 On page 38 of this submission, you state that "Rifaximin will be compared to Cipro with respect to TLUS using the Cox proportional hazards model (Wald statistic) using a one-sided test at a significance level of 0 05 " We recommend that one sided-tests be performed at an alpha level of 0 025

5 If you use over-encapsulation of study drug, you will need to demonstrate that encapsulation of the rifaximin and CIPRO® tablets in Study RFID3001 does not alter bioavailability Please consider the following options

a You could use the double dummy design by utilizing rifaximin placebo in a tablet dosage form and ciprofloxacin placebo in a tablet dosage form In this double-dummy design, the rifaximin-treated group would receive a rifaximin regimen and placebo "ciprofloxacin" tablets The ciprofloxacin-treated group would receive CIPRO® tablets and a placebo "rifaximin" regimen The placebo-treated patients would receive placebo "ciprofloxacin" and placebo "rifaximin" tablets

b If you use the planned design in the submitted protocol RIFD3001, you need to ensure that the encapsulated tablets are equivalent to the respective unencapsulated tablets To verify that encapsulation of the tablets does not alter drug release, you should perform dissolution testing comparing the encapsulated tablets to the unencapsulated tablets Rifaximin dissolution should be tested using the medium used in the method submitted in NDA 21-361 and two other media of varying pH CIPRO® dissolution should be tested using the USP dissolution method and two other media of varying pH The data submitted should include comparisons of the dissolution profiles using the f2 metric

c An additional bioequivalence study may be needed if the dissolution testing is not acceptable

We remind you that these comments are intended to reflect our review of the protocol for Study RFID3001 only The review of your NDA 21-361 for Lumenax™ Tablets is on-

going While we have attempted to inform you of issues relevant to your proposed protocol that we are aware of at this point in our review, we cannot at this point in time identify all of the potential deficiencies that may exist within NDA 21-361 We bring this to your attention because when we have completed our review of NDA 21-361 it is possible that there may be deficiencies in NDA 21-361 that your Study RFID3001 may not address It is also important to note that deficiencies outside of the realm of what Study RFID3001 could be expected to address may also be identified during the review of NDA 21-361

Please contact me at (301) 827-2485 if you have any questions regarding the above

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Jouhayna Salıba
3/27/02 03 33 56 PM
CSO
for Dıana Wıllard (IND 52,980)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE March 15, 2002

To /	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number /	**Fax Number** 301-827-2475
Phone Number /	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 2

We have the following requests regarding NDA 21-361

1 In RFID9701, please explain the discrepancies between the datasets ENRLSUM and FOLLOWUP for the variable TLUS

2 In RFID9801, please verify the proportional hazards model used for the Rifaximin 400 TID versus Placebo analysis We believe treatment was incorrectly coded Also, the confidence intervals about the hazard ratio reported for both treatment comparisons are not two-sided Please revise Table 17 of the study report with two-sided 97 5% confidence intervals and the results for the proportional hazards model

Please contact me at (301) 827-2485 if you have any questions regarding the above comments

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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Diana Willard
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Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE March 14, 2002

To /	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number \	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 3

We have the following requests regarding NDA 21-361

1 We are unable to make any decision concerning the adequacy of the stability data or the expiration dating period without full details of the commercial container-closure systems utilizing bottles Please also supply details of the packaging materials for the primary stability batches manufactured by Alfa Wasserman and the commercial batches manufactured by any way? Please describe the secondary packaging for all packaging configurations and supply samples of container labels and carton artwork You may wish to refer to the Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation published in May 1999 and available at http //www fda gov/cder/guidance/index htm

2 Please clarify the tests that are performed on the drug substance when it arrives at the drug product manufacturing plant

3 Please describe the particle size distributions in the batches of drug substance that were used to make the drug product to be used in the clinical trials Please also

describe the particle size distributions in the batches of drug substance that are used to make the commercial drug product manufactured by

4 In Table 51 you describe the equipment that will use for the scale batches Please describe the equipment that will use for the commercial scale lots

5 As suggested in ICH Q6A, please consider adding a second identity test to the drug product specifications

Please contact me at (301) 827-2485 if you have any questions regarding the above comments

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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

/s/

Diana Willard
3/14/02 09 24 37 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE March 5, 2002

To /	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number /	**Fax Number** 301-827-2475
Phone Number /	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 2

We have the following request from our Clinical Pharmacology & Biopharmaceutics reviewer regarding your NDA 21-361

> Please submit the components and composition of Baycip If you are unable to obtain this information directly from the sponsor of this formulation, then please have the sponsor of Baycip submit the requested information directly to the FDA Also, it is requested that you obtain a letter of authorization from Bayer US allowing the Agency to reference the Cipro NDA for the components and composition of that formulation

Please contact me at (301) 827-2485 if you have any questions regarding the above request

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
3/5/02 08 39 26 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE February 20, 2002

To	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number /	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 2

We have the following request from our Clinical Pharmacology & Biopharmaceutics reviewer regarding your NDA 21-361

> Please submit the components and composition of Plenolyt (as discussed at the January 19, 2001 teleconference between Salix and the FDA) If you are unable to obtain this information directly from the sponsor of this formulation, then please have the sponsor of Plenolyt submit the requested information directly to the FDA

Please contact me at (301) 827-2485 if you have any questions regarding the above request

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
2/20/02 10 50 03 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE February 1, 2002

To	**From** Diana M Willard
Company Salix Pharmaceuticals, Inc	Division of Special Pathogen and Immunologic Drug Products
Fax Number	**Fax Number** 301-827-2475
Phone Number	**Phone Number** 301-827-2485

Subject NDA 21-361/Lumenax™ (rifaximin) Tablets

Total no of pages including cover 1

We have the following requests regarding NDA 21-361

Please confirm that the following facilities are the ONLY sites involved in the manufacturing, testing and packaging of drug substance and drug product for your NDA 21-361 Please confirm that the address and the functions listed for each site are correct, and that all the facilities are ready for the GMP inspection

Drug substance (rifaximin)

1

Drug product (rifaximin tablets)

1

2

3

Additionally, please commit to notifying the Division if you are informed by the — — that any amendments have been submitted to DMF — for —

Please contact me at (301) 827-2485 if you have any questions regarding the above comments

Diana Willard, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Diana Willard
2/1/02 03 14 03 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-361	Efficacy Supplement Type n/a	Supplement Number n/a	
Drug Xifaxan™ (rifaximin) Tablets, 200 mg		Applicant Salix Pharmaceuticals, Inc	
RPM Andrei Nabakowski		HFD-590	Phone # 301-827-2424
Application Type (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name) N/A	

❖ Application Classifications	
• Review priority	**(X) Standard ( ) Priority**
• Chem class (NDAs only)	**1 (NME)**
• Other (e g , orphan, OTC)	N/A
❖ User Fee Goal Dates	May 26, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314 510 (accelerated approval) ( ) 21 CFR 314 520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification verified that qualifying language (e g , willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent	(X) Verified
❖ Patent	
• Information Verify that form FDA-3542a was submitted	(X) Verified
• Patent certification [505(b)(2) applications] Verify type of certifications submitted	21 CFR 314 50(i)(1)(i)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314 50(i)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice)	( ) Verified N/A

❖ Exclusivi (approvals only)	
• Exclusivity summary	**X (5 years- NME)**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316 3(b)(13) for the definition of sameness for an orphan drug (i e active moiety) This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 10/25/02
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division s proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS reviews 5/6/02, 9/25/02, 4/1/04, 5/7/04, labeling meetings 4/30/04, 5/5/04
• Other relevant labeling (e g , most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	X (DMETS and CMC reviews)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A – none requested
• Documentation of discussions and/or agreements relating to post marketing commitments	N/A
❖ Outgoing correspondence (i e , letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	9/21/98
• Pre-NDA meeting (indicate date)	1/12/01
• Pre-Approval Safety Conference (indicate date, approvals only)	5/13/04 memo
• Other	X

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e g , Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	TL – 10/25/02, 5/24/04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/25/02, 5/21/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	3/14/02, 5/21/04
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	5/8/02, 5/20/04
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	PSC memo- 5/13/04
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	5/13/04
❖ Statistical review(s) *(indicate date for each review)*	9/17/02 5/3/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11/5/02 5/7/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/23/02
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10/28/02, 10/30/02, 5/13/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/30/02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed 3/11/04 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2/4/03, 5/5/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

USER FEE VALIDATION SHEET

NDA # 21-361 ~~Supp Type &~~ # N000 UFID # 4102
(e g , N000, SLR001. SE1001, etc)

1 YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s)

2 (YES) NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e g to add an adverse reaction contraindication or warning to the labeling)

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION

3 YES (NO) SMALL BUSINESS EXEMPTION

4 YES (NO) WAIVER GRANTED

5 YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling)
If YES list all NDA #s review division(s) and those for which an application fee applies

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6 (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement If NO, list resulting NDA #s and review division(s)

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7 P (S) PRIORITY or STANDARD APPLICATION?

151
PM Signature / Date

12/28/01
CPMS Concurrence Signature / Date

2/14/00

N2311

RIFAXIMIN

1 12 ITEM18 USER FEE COVER SHEET

ITEM 18 User Fee Cover Sheet

The User Fee I D Number assigned to NDA 21-361, Rifaximin, is 4102 The User Fee Cover Sheet (Form FDA 3397) is attached Also included is copy of the check number 6358, in the amount of $309,647 00, as evidence of payment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date February 29 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side If payment is sent by U S mail or courier please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website http://www fda gov/cder/pdufa/default.htm

1 APPLICANT'S NAME AND ADDRESS

Salix Pharmaceuticals, Inc
Attention Lorin Johnson, PhD
3600 West Bayshore Road
Palo Alto, CA 94303

2. TELEPHONE NUMBER *(Include Area Code)*

(650) 849-5900

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-361

5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT STOP HERE AND SIGN THIS FORM

IF RESPONSE IS 'YES' CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO

(APPLICATION NO CONTAINING THE DATA)

3 PRODUCT NAME

LUMENAX (rifaximin) tablets

6 USER FEE I D NUMBER

4102

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD DRUG AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7 reverse side before checking box)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food Drug and Cosmetic Act *(See item 7 reverse side before checking box)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food Drug and Cosmetic Act *(See item 7 reverse side before checking box)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8 reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response including the time for reviewing instructions searching existing data sources gathering and maintaining the data needed and completing and reviewing the collection of information Send comments regarding this burden estimate or any other aspect of this collection of information including suggestions for reducing this burden to

Department of Health and Human Services
Food and Drug Administration
CBER HFM 99
1401 Rockville Pike
Rockville MD 20852 1448

and

Food and Drug Administration
CDER HFD 94
12420 Parklawn Drive Room 3046
Rockville MD 20852

An agency may not conduct or sponsor and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Sr VP Development & Chief Scientific Officer	11/21/01

FORM FDA 3397 (4/01)

7 Page(s) Withheld