

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-361**

**CORRESPONDENCE**



NDA 21-361

Salix Pharmaceuticals, Inc  
Attention Lorin K Johnson, Ph D  
Sr Vice President and Chief Scientific Officer  
3600 West Bayshore Road  
Palo Alto, CA 94303

Dear Dr Johnson

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

Name of Drug Product	Lumenax (rifaximin) Tablet
Review Priority Classification	Standard (S)
Date of Application	December 21, 2001
Date of Receipt	December 26, 2001
Our Reference Number	NDA 21-361

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 24, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the User Fee goal date will be October 25, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at

[www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric) and contact the Division for details

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic  
Drug Products, HFD-590  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic  
Drug Products, HFD-590  
Attention: Division Document Room  
9201 Corporate Blvd  
Rockville, Maryland 20850-3202

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Ellen C. Frank, R.Ph.  
Chief, Project Management Staff  
Division of Special Pathogen and Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Ellen Frank  
1/3/02 09 50 10 PM  
NDA 21-361



IND 52,980

Salix Pharmaceuticals, Inc  
Attention Mr  
3600 West Bayshore Road  
Suite 250  
Palo Alto, CA 94303

Dear Mr

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 your amendments dated November 2, and December 10, 2001, serial numbers 055 and 056, containing clinical microbiology data and to the December 7, 2001 teleconference between Salix and this Division

We have reviewed these submissions and have the following comments that we believe summarize our December 7, 2001 discussion

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- 2 Upon examination of the preliminary information that you have submitted, we still question how your data will be able to provide sufficient support for the dose you have selected (200 mg po tid) because your studies were performed using different dosages and dosing regimens
- 3 During the NDA review process, we will review the data from the clinical studies submitted in the application. We may identify additional deficiencies during the course of the review. To address such deficiencies, it is possible that that you may need to do additional studies. Please note that the approvability of an NDA depends on a complete review of the NDA.
- 4 You may amend your application during the course of the review cycle with additional data, however, you should be aware that we may not be able to review the amendment during the same review cycle.

- 5 If you wish to conduct an additional adequate and well-controlled study to support your planned application, we would be willing to review your protocol before the study is initiated

We suggest that you consider a three-arm study including the proposed dosage regimen you intend to market, a placebo regimen, and an active-control regimen

The final study report and supporting documentation should be provided, and the information from the additional study should be integrated with the efficacy data and the safety data from the studies already conducted. As noted in item 4 above, if you amend your application with the data from this study, you should be aware that we may not be able to review the amendment during the same review cycle.

- 6 We remind you that you need to provide data supporting the comparability of the rifaximin formulations used in your clinical studies to the formulation proposed for approval. This data should include comparisons of dissolution profiles using the  $f_2$  metric.
- 7 We also remind you that you need to provide information establishing a bio-link between the Spanish generic formulation of ciprofloxacin that was used in one of your clinical studies by submitting the following information (as requested during the January 19, 2001 teleconference)

- the study report for the human bioequivalence study linking the Spanish generic ciprofloxacin formulation used in your study to the Spanish Bayer ciprofloxacin formulation,

and

- the components and composition as well as comparative full dissolution data profiles using the  $f_2$  metric to provide a link between the Spanish Bayer ciprofloxacin formulation and the approved US Bayer ciprofloxacin formulation

If, after considering these comments, you choose to submit your New Drug Application, we anticipate we would file it according to 314.101. We would complete our review within the pertinent time frame as specified in the 1997 PDUFA Reauthorization Performance Goals and Procedures. We would then provide an approval, approvable or not approvable letter based upon the findings of our review. These three types of letters are described at 21 CFR 314.105, 21 CFR 314.110, and 21 CFR 314.120, respectively.

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 reports (21 CFR 312.33).

If you have any questions, contact Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

*{See appended electronic signature page}*

**Renata Albrecht, M D**  
**Acting Director**  
**Division of Special Pathogen and**  
**Immunologic Drug Products**  
**Office of Drug Evaluation IV**  
**Center for Drug Evaluation and Research**

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/s/

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Renata Albrecht  
12/14/01 05 46 01 PM  
IND 52980

Sponsor's Meeting Minutes for  
End of Phase II Meeting

S A L I X  
Pharmaceuticals Inc

October 20, 1998

Mark Goldberger, MD, MPH  
Division of Special Pathogens and Immunologic Drug Products HFD-590  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Attention Document Control Room  
5600 Fishers Lane  
Rockville, MD 20857

IND 52 980/#011  
/ (rifaximin) Tablets

Minutes of September 21, 1998 Meeting

Dear Dr Goldberger,

We would like to thank the FDA representatives for their time and consideration in meeting with us on September 21, 1998 to discuss the proposed development program for rifaximin in the treatment of (traveler's) diarrhea. As a follow-up to this meeting please find enclosed minutes of the meeting and a specific proposal for addressing FDA's request for an intravenous rabbit teratology study

Meeting Minutes

We have prepared minutes of this meeting that we believe accurately reflect the discussions and enclose them for your review. We also make reference to the meeting background document submitted in serial #010 to this IND on August 28, 1998 and the discussion questions included in this document. These discussion questions were the basis of the September 21 meeting and are attached to the meeting minutes for your convenience. Please contact us to clarify any points that are not clear or not in accordance with the Division's understanding of the meeting discussions. We also look forward to receipt of the Division's meeting minutes.

The intent of the meeting was to obtain clarification on the additional studies that would be required for submission of an NDA for rifaximin in the treatment of (traveler's) diarrhea, as a potential first submission,

Salix recognizes the need for the additional studies, protocols, or data from CMC, Toxicology, Microbiology, and Pharmacokinetics as defined in the minutes submitted herein or the presentations made at the meeting (overheads presented at the meeting are attached)

It is Salix's understanding that one additional proposed Phase III clinical trial will be sufficient to support a claim of efficacy in the treatment of — 'traveler's) diarrhea, provided safety data are available for at least 500 patients treated with the same or higher doses. Safety data in regulatory submissions to support subsequent indications would have to achieve the same minimum safety database requirement.

Salix intends to work with FDA on the statistical analysis plan of the recently completed infectious diarrhea study and the planned Phase III trial. We appreciate FDA's input in helping us design the analyses and the study design to focus on regulatory requirements (please see FDA Statistical Comments below).

Rabbit Segment II Intravenous Teratology Study

In the meeting of September 21, 1998, FDA suggested that

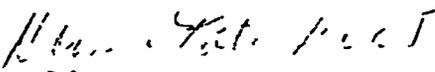
Upon further consideration of this request, Salix would like clarification on whether this study would be required for the NDA submission. Alternatively, Salix would be willing to accept Pregnancy Category C rifamycin-class labeling or equivalent labeling since the molecule is structurally related to rifampin. Such labeling would be acceptable to Salix for now, with the understanding that performing the

FDA Statistical Comments

We acknowledge receipt of FDA's fax of October 9, 1998 containing FDA's statistical comments from the September 21, 1998 meeting and additional comments on the Phase III comparative study with ciprofloxacin (which has not been unblinded and analyzed) and the planned Phase III study versus placebo. We are currently drafting the analysis plan for the comparative study with ciprofloxacin and will submit it soon, along with a response to the comments requested by FDA. We anticipate to submit the protocol and analysis plan for the placebo-controlled study at the same time.

If you have any questions about the enclosed material, please do not hesitate to call me at (650) 849-5900.

Sincerely,

  
Lorin Johnson  
Vice President, Research



**Salix Pharmaceuticals, Inc**  
**Minutes of Meeting with FDA**  
**21 September, 1998**

A meeting was held on 21 September, 1998 from 3-5 PM at 9201 Corporate Blvd. Conference Rooms S400, Rockville, MD, between representatives of Salix and the FDA Division of Special Pathogens and Immunologic Drug Products, with attendees from additional FDA Divisions present. The purpose of the meeting was to discuss the development program for rifaximin under IND 52,980 to treat \_\_\_\_\_ (traveler's) diarrhea, \_\_\_\_\_

Prior to the meeting, Salix submitted a list of questions that they wanted FDA responses to and a background document summarizing rifaximin development to date. The questions are appended to this document, together with a list of attendees.

Salix recognizes that FDA expects Salix to conduct all studies suggested in the background document and in the presentation.

Following introductions, Ms Atkins of FDA stated that there was a small change to the proposed agenda, as one of the FDA personnel had to leave. Thus, CMC issues were addressed prior to the presentation by Salix.

**I Chemistry, Manufacturing and Controls**

Question 1 in Section 1 B addressed methods to show the comparability of product used in clinical trials to date and that to be used in the proposed clinical studies by using in vitro dissolution studies. The following points were made:

- The plan was acceptable to FDA, provided dissolution profiles were established in multiple media (three). FDA wished to review the protocols, looking at apparatus, media, and profile over multiple time points.
- The most concern was to link the product used in the proposed Phase III study and commercial product.
- The acceptance of the plan was based on using the same formulation and the same manufacturing procedure as used in the European product. (Salix said the manufacturing and formulation were the same.)
- Stability protocols would be needed later, as per ICH guideline, FDA wanted one-year stability as a minimum at the time of NDA submission.

## II. Presentation by Salix

Dr Lise Riopel	Objectives of the Meeting
Dr Herbert DuPont	Treatment of Traveler's Diarrhea
—	Introduction to Rifaximin
Dr Lise Riopel	Proposed Clinical Study
—	Microbiology Issues

- FDA asked why rifaximin was so little absorbed. Salix replied the only difference between rifaximin and rifampin was in a single area of the molecule near the bottom, so this had to be responsible.

## III General Discussion and Questions

- FDA questioned whether the three proposed clinical sites would show differences in the pathogens. Dr DuPont (Salix's clinical consultant) replied that the predominant pathogen in Kenya and Mexico would be ETEC (enterotoxigenic Escherichia coli) and Campylobacter would predominate in Thailand.
- FDA asked if the sites would be the same size, Salix replied they were expected to enroll comparable numbers of patients.
- FDA asked if any of the sites had been used before. Salix replied Dr DuPont's site had been involved in two previous studies of rifaximin. The site in Kenya was run by Professor [redacted], a well-respected investigator in the medical area. The site in Thailand would be under the auspices of [redacted].
- FDA questioned whether the proposed Phase III study was powered to show a difference within each site, as the bacterial pathogens might differ. Salix replied the study was not so powered, but there was randomization by site to treatment group.
- FDA asked about bid dosing and why it was not considered. (During the presentation, Salix presented Dr DuPont's current trial with bid dosing as supportive evidence, but stated Salix did not intend to pursue bid dosing.) Dr DuPont replied he believed a drug such as rifaximin, which was not absorbed, would be washed out by the diarrhea, whereas ciprofloxacin was absorbed so there was a continuous reservoir of drug. The current trial was designed as a marketing study (for Europe) to compete with the bid dosing of ciprofloxacin.

- FDA questioned whether there were any data on the use of antimotility agents, such as Lomotil, to stop the diarrhea and increase the antibiotic concentration in the intestines. Dr. DuPont replied he had never considered this idea. The assumption had been combination therapy worked better because of a joint attack on symptoms and pathogens.
- FDA stated the issues related to transferable resistance were not clear. Salix responded that the mechanism of resistance by rifampin and rifaximin was the same.
- FDA asked what studies would be used in the NDA. Salix responded that the Phase II and III DuPont studies would be submitted along with the proposed Phase III trial. Salix also would use the existing studies from Europe as supportive evidence. FDA responded that that was their interpretation of Salix's intent and agreed that the one proposed additional well-controlled phase III study will be sufficient to meet the NDA requirement for this indication.

#### IV Pharmacology and Toxicology

- Section 1 C. FDA stated the animal pharmacology studies were sufficient.
- Section 1 E. FDA stated the current and proposed studies would appear to meet the requirements, pending receipt and review of the studies.
- FDA stated they had not seen the 4-week toxicity studies but Salix said that these reports were submitted.

*Post meeting note: Salix confirms that these reports were submitted on June 23, 1998, serial #004.*

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- FDA commented that the reproductive and genetic studies generally appeared to be adequate. However, Salix should be prepared to demonstrate comparable negative absorption of rifaximin in humans and animals. The rifampins have teratogenic effects. Therefore, Salix might have to 

## V. Microbiology

- FDA stated they wanted pre and post treatment fecal sample collected in the proposed clinical study, with pathogens cultured and MICs determined. Dr DuPont stated he collected pre and day 5 pathogens and performed MIC determinations using NCCLS methods. FDA stated they wished to receive and review a copy of the methods. Salix agreed.

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- FDA stated that the same microbiological protocol and the same breakpoints should be used at all laboratories in the Phase III study. Salix agreed to provide the protocol. Samples from Kenya would probably be sent to Dr DuPont's laboratory and Thailand would use the

## VI Clinical – Statistical

- FDA stated the clinical trials looked okay in general. From the discussion later, four major points are extracted:
  - a FDA wants to review the statistical analysis plan for Dr DuPont's ciprofloxacin-comparative study before the blind is broken.
  - b FDA wants a full protocol before the Phase III study is commenced and all endpoints and analyses should be clarified.
  - c FDA questioned the power of the study, it was powered on a proportion analysis, whereas the time to end of diarrhea was a survival analysis. FDA stated that with four treatment groups using a Bonferroni correction, sample size should be about 350 patients (lowered if the high-dose group was removed). A follow-up teleconference was recommended.
  - d There is little reason to pursue the 1800 mg/day group.

- FDA questioned what the endpoint for analysis was in the proposed study
  - (a) time diarrhea stopped, or
  - (b) effect at some timepoint Salix replied the primary endpoint was the proportion of patients cured at the end of the treatment period.
- There was question about the proposed endpoint of TLUS (time to last unformed stool) and what it meant Dr DuPont deferred to his published definition of wellness Dr Albrecht (FDA) read the definition from Dr DuPont s article
- Following discussion, FDA agreed that a clinical definition, or a practical one (Dr Goldberger stated that the end of diarrhea was much more important to a traveler than how many were cured by some timepoint) should be included Thus, both analysis endpoints should be pursued
- Salix intended to start the clinical trial in late 1998 or early 1999 Later discussion of the time to NDA indicated early 2000
- FDA questioned whether there would be enough pathogens other than ETEC isolated in the studies as ETEC was the bulk in Kenya and Mexico, although Campylobacter would predominate in Thailand Dr DuPont felt that between the three sites there would be enough Shigella and Salmonella isolated
- FDA stated the actual labeling would be based on the pathogens isolated
- Salix responded they intended to label for diarrhea

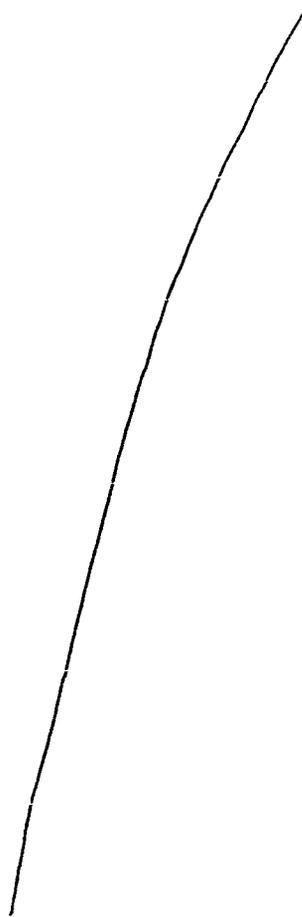
## V Safety Issues

Dr Goldberger, Division Director of Special Pathogens, stated that the minimum safety database would be 500 patients, treated at the proposed labeling dose or higher doses Safety information with longer treatment, at higher doses, or in more severe patients (e g , Hepatic Encephalopathy) would be welcomed The following points were made

- Publications are not sufficient
  - Clinical Study Reports should be submitted, with CRFs available, if needed.
  - Not every study needs a report, if FDA accepts the results
  - Salix should provide FDA with information on what can be done with the data from the past and present studies for the safety database

## **VI Pharmacokinetics**

- FDA stated they wanted the major metabolite(s) used in the in vitro induction and inhibition assay in human liver microsomes/hepatocytes in addition to the rifaximin
- FDA stated a single-dose food-effect study was needed The study should also examine the urinary metabolite levels
- FDA stated that intestinal metabolism of rifaximin might be an issue



## **XI Manufacturing**

- A final discussion indicated Alfa Wassermann, who makes the drug substance, might manufacture the drug product in Italy. Stability data would be required on this drug product in the NDA.

**SIGN IN SHEET FOR ATTENDEES**

Monday, September 21, 1998

3:00 pm - 5:00 pm

Room 9400

920 Corporate Boulevard

Salix Pharmaceuticals

*MD* Herbert DuPont, M.D. clinical consultant to Salix  
microbiology consultant to Salix  
microbiology consultant to Salix  
scientist and regulatory consultant to Salix

*DB* David Doyle, Executive VP Salix  
*LJ* Larn Johnson, Ph.D., VP of Research, Salix  
*PH* Ping Hsu, Ph.D., Director of Biostatistics and Data Management, Salix  
*SV* Live Project Ph.D. Molecular Cell & Studies

Food and Drug Administration

Director of Special Pathogen and Immunologic Drug Products (DSPIDP)

Mark Goldberger M.D., M.P.H., Director

Renata Albrecht M.D. Deputy Director

Marc Cavalliti-Coll M.D. Medical Team Leader

Rigoberto Roca, M.D., Medical Officer *HR*

*BI* Norman Schuff, Ph.D., Chemistry Team Leader

John Smith, Ph.D., Chemistry Reviewer

Nancy Sillman, Ph.D., Statistical Team Leader

Cheryl Dixon, Ph.D. Statistical Reviewer

Fumilayo Ajayi Ph.D., Clin. Pharm. & Biopharmaceutics Team Leader

Philip Colangelo Ph.D., Reviewing Clin. Pharm. & Biopharmaceutics Officer

Kenneth Hastings, Ph.D., Pharmacology Team Leader

Steve Kunder Ph.D. Pharm/Tox Reviewer

Sheri Lard, Ph.D., Microbiology Team Leader

Linda Uttrup, Ph.D., Microbiology Reviewer

Peter Dionne, Microbiology Reviewer

Linda Gosev B.S., Microbiology Reviewer

Brenda Atkins, B.S. Project Manager

*Ellen C. Frank, CPMS*

*HOWDA MONTAGNE, PK Reviewer*  
of Anti-Infective Drug Products

Gary Chikani, M.D., Division Director

Division of Anti-viral Drug Products:

*BI* Harry O'Hanlon, Ph.D., Microbiology Reviewer

Division of Gastro-Intestinal and Coagulation Drug Products:

*BI* John Sensor M.D. Medical Officer

1. EXECUTIVE SUMMARY AND DISCUSSION POINTS

1.1 BACKGROUND

This submission is intended to be reviewed in advance of a meeting with the Division of Special Pathogens on September 21 1998 at 3 PM. The purpose of this meeting is to discuss the development of rifaximin in the treatment of \_\_\_\_\_ diarrhea \_\_\_\_\_

Specifically we are requesting the Division's comments on the adequacy of the data obtained to date in meeting the requirements of an NDA in the treatment of \_\_\_\_\_ diarrhea and comments on the design of a proposed Phase III trial

To help guide the discussion we have prepared lists of questions to be addressed during the meeting. These questions are listed below by NDA section

Rifaximin is licensed from Alfa-Wassermann in Italy and has been marketed in Italy since 1988 and in several other countries for the treatment of infectious diarrhea, hepatic encephalopathy, as well as for other indications affecting the gastrointestinal tract (see Section 4). Salix obtained North American licensing rights to the product and has pursued the development of this drug in the United States IND 52 980 \_\_\_\_\_ but no patients have been treated to date. Salix received orphan drug designation on February 10 1998 from the Office of Orphan Products to develop rifaximin for the treatment of hepatic encephalopathy \_\_\_\_\_

To date our licensing partner Alfa Wassermann has conducted most of the development work for rifaximin in Europe and in Latin America. We have summarized the results in this document and propose that they are sufficient together with a single additional well-controlled U.S. Phase III trial, to meet the requirements for an approvable NDA in \_\_\_\_\_ diarrhea

## 1 B CHEMISTRY, MANUFACTURING AND CONTROLS

Alfa Wassermann has manufactured  (rifaximin) oral tablets for commercial distribution for over 10 years. The manufacturing process is well-defined and consists of adequate controls to ensure the safety, identity, quality, strength, and purity of the drug. Clinical studies conducted to date have utilized drug manufactured by Alfa-Wassermann in Italy. These studies include a completed Phase II dose-ranging study in patients with traveler's diarrhea (DuPont), an ongoing Phase III comparative study versus ciprofloxacin in patients with traveler's diarrhea (DuPont), and the published studies in over 1400 patients treated for various infections of the GI tract. Salix plans to manufacture clinical supplies for future clinical studies, including the proposed Phase III study in patients with traveler's diarrhea, at a U.S. contract manufacturer following the same manufacturing and formulation procedures and processes as those used by Alfa-Wassermann. The commercial manufacturer has yet to be determined.

### Discussion Points

1. To show that the two manufacturers are producing the same product, we plan to conduct stability studies including *in vitro* dissolution studies, to provide a link between drug used in the clinical studies conducted to date and drug being manufactured for the proposed clinical study. This recommendation was made by the GI Division at our April 30 meeting. Please give us your comments on the acceptability of this plan.

## 1 C ANIMAL PHARMACOLOGY

The pharmacological effects of rifaximin have been well-characterized in a number of animal models and the drug was shown to have no effects on any body system except at very high doses (i.e., 1000 mg/kg/day). In addition, the antimicrobial action of rifaximin has been evaluated in a series of *in vitro* experiments, which demonstrated that it has a wide spectrum of antimicrobial activity with activity against both gram-negative and gram-positive bacteria.

Single and multiple dose pharmacokinetic studies in rats and dogs by the IV and oral routes show that the drug is 1) rapidly cleared from the body after IV or oral administration, 2) minimally absorbed into the systemic circulation after oral administration, and 3) is primarily eliminated in the feces. Studies of radiolabeled rifaximin in rats confirm that most of the drug remains in the GI tract after oral administration.

### Discussion Points

- 1 We wish to confirm the adequacy of the animal pharmacology studies to meet the requirements for an NDA in — diarrhea —

### I D MICROBIOLOGY

One of the concerns with rifaximin, since it is a member of the rifamycin class of antimicrobials is the development of resistance to this agent and cross-resistance to rifampin. The development of resistance or cross-resistance to rifampin is of concern especially in patients infected with *Mycobacterium tuberculosis*. This document contains summaries of *in vitro* and *in vivo* animal studies indicating that rifaximin does not induce cross-resistance to rifampicin. To provide additional information on the issue of the development of resistance a clinical study is planned which will evaluate the colonic flora before, during, and after 3 cycles of a 10-day course of treatment in ulcerative colitis patients.

Additional *in vitro* studies of resistance and cross resistance have been completed or are planned as suggested by the FDA's microbiology reviewers during the meeting of April 30, 1998. The current document summarizes the results of studies to determine the MICs for 10 or more clinical isolates of several Gram-positive, Gram-negative, and anaerobic species from 3 geographically distinct locations in the U.S. and one in Canada. This information was requested at the April 30 meeting and is included herein. In a proposed study, the MICs for rifaximin and rifampin will be compared and the frequency of spontaneously occurring mutants resistant to rifaximin or rifampin will be determined. It was requested that the minimum bactericidal concentration (MBC) of rifaximin be determined. Some data are available on MBC and are summarized herein. Finally, the development of resistance following serial transfers of increasing concentrations of drug will be examined. Some data are presented herein, but may not be adequate.

Fecal microbiological determinations were made before and after treatment in a number of clinical trials of rifaximin in infectious diarrhea. These studies demonstrated the eradication of most pathogens as a result of treatment. In placebo-controlled trials, rifaximin was superior to placebo in eradicating organisms and achieving clinical cures. These data are presented in this document. Microbiological assessments will also be conducted in the proposed Phase III study.

Discussion Points

- 1 We wish to confirm the adequacy of these studies to meet the requirements of an FDA in diarrhea
- 2 We wish to confirm whether the additional data on MICs for US clinical isolates, and other isolates are sufficient
- 3 We wish to confirm whether the additional data on MBC are sufficient

1 E NONCLINICAL TOXICOLOGY

A complete series of toxicology studies (including acute, subchronic chronic, and reproductive toxicology) was conducted by Alfa Wassermann in the early 1980 s prior to the adoption of GLPs in Italy. These studies were scientifically well executed, as attention was given to protocols, animal housing, experience of the investigators, the number and size of the experimental groups, and the characterization of the test article and thus conform with the spirit of GLP. In the late 1980s, a standard battery of GLP-compliant mutagenicity studies was conducted. These repeat studies confirm the earlier results showing that rifaximin is negative for mutagenicity. In addition, GLP-compliant subchronic (4-week) preliminary toxicity studies were recently conducted in rats and dogs and a teratology (preliminary and final) study was conducted in rabbits. The results of these studies confirm the results of the earlier studies showing that oral rifaximin has little toxicity.

Per our discussions with FDA's GI Division on April 30, it was stated that the 13-week toxicity studies would have to be repeated using higher doses and a sufficient number of animals per dose group. In addition, the GI Division requested that the reproductive studies be repeated and a Chinese hamster ovary test (or mouse lymphoma test) be repeated with non-cytotoxic doses. Instead of the 13-week studies, Salix is planning to submit data from 6-month rat (maximum dose 300 mg/kg/day) and 9-month dog (maximum dose 1000 mg/kg/day) chronic toxicity studies conducted at a contract laboratory according to current GLP standards.

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1 F CLINICAL

A number of studies in patients with infectious diarrhea and other infections have been conducted and published by Alfa-Wassermann and others in Italy. Rifaximin has been administered to over 1465 subjects in over 40 clinical trials (Table 1)

These studies include several controlled and uncontrolled studies that provide evidence of the safety and efficacy of the drug in over 350 patients with infectious diarrhea. Patient data are available from most of these published studies. This includes one Phase II dose-ranging study that was recently completed in Mexico for traveler's diarrhea. Another Phase III study in traveler's diarrhea is currently underway.

Table 1 Exposure to Rifaximin in Clinical Trials

Disease	Number of Patients	Adverse Events
Acute infectious diarrhea	133	Urticarial rash (1)
Traveler's diarrhea	55	None
	93	Vomiting (2), D/C
	63	None
	1	None
	10	None
	254	None
	20	None
	335	Diarrhea (2), nausea (1)
	10	None
Ulcerative colitis	12	None
	20	None
Hepatic encephalopathy	400	See Section 9 F
TOTAL	1465 <sup>a</sup>	

a Does not include patients enrolled in ongoing trials

Based on the results from these clinical studies and the post-marketing pharmacovigilance conducted in Italy, rifaximin appears to be effective and well-tolerated.

We propose that these studies adequately demonstrate the safety and efficacy of rifaximin for the treatment of patients with infectious diarrhea and together with one other Phase III study would be sufficient for an NDA in this indication.

Discussion Points

1 In the NDA for [redacted] diarrhea we are planning to submit the results of one Phase II dose-ranging study in patients with traveler's diarrhea (DuPont), a Phase III comparative study versus ciprofloxacin in patients with traveler's diarrhea (DuPont see protocol in Appendix A) and one additional proposed Phase III study in [redacted] traveler's diarrhea (see Appendix B) as adequate support for the assessment of the safety and efficacy of rifaximin in the treatment of patients with [redacted] diarrhea [redacted]

/ Please provide your comments on the adequacy of these studies in fulfilling the requirements of an NDA in this indication

2 To date rifaximin has been administered to approximately 1465 patients for the treatment of various bacterial conditions, mostly in the gastrointestinal tract, at dose regimens up to 2400 mg/day for up to 10 days. Over 200 patients with [redacted] have been treated for 7 days/month for  $\geq 6$  months (180 patients for up to 1 year). We propose that the clinical safety information accumulated to date along with data from the ongoing and proposed Phase III studies in traveler's diarrhea are adequate for demonstrating the safety of rifaximin in an NDA for [redacted] diarrhea. Please provide your comments on this proposal

3 Pharmacokinetic studies conducted to date show that orally administered rifaximin is largely not absorbed from the GI tract and is largely eliminated in the feces. The plasma levels of drug are either below the limit of detection or present at very low concentrations for the first few hours after oral dosing. A small fraction of the dose is excreted in the urine. We wish to confirm the adequacy of the completed pharmacokinetic studies for an NDA for the treatment of [redacted] diarrhea patients with rifaximin

4 The primary efficacy variable in the proposed Phase III study will be the time to last unformed stool (TLUS), from which the response rate is defined as the proportion of patients with passage of last unformed stool during the treatment period. The secondary efficacy will include bacteriological cure and improvement of diarrheal syndrome. Please confirm that these endpoints are acceptable

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**Attachment 3. FDA fax dated October 1, 1999 concerning clarification September 28, 1998 meeting minutes**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

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