CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-361

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-361

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

Dear Mr Kashiwase

Please refer to your new drug application (NDA) dated December 21, 2001, received December 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xifaxan™ (rifaximin) Tablets 200 mg

We acknowledge receipt of your submissions dated

October 30, 2002
May 2, 2003
October 7, 2003
October 31, 2003
November 24, 2003
November 25, 2003 (2)
December 9, 2003
January 20, 2004
February 5, 2004
February 25, 2004
March 17, 2004
April 12, 2004
April 21, 2004
April 22, 2004
April 26, 2004
April 29, 2004
May 4, 2004
May 12, 2004
May 17, 2004
May 19, 2004
May 21, 2004

The November 25, 2003 submission constituted a complete response to our October 25, 2002 action letter

This new drug application provides for the use of Xifaxan™ (rifaximin) Tablets 200 mg for the following indication

> Xifaxan™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*
>
> Xifaxan™ Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*

We completed our review of this application, as amended It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted labeling (immediate container and carton labels) submitted May 21, 2004 Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed Individually mount 15 of the copies on heavy-weight paper or similar material For administrative purposes, designate this submission "**FPL for approved NDA 21-361** " Approval of this submission by FDA is not required before the labeling is used

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 We are waiving the pediatric study requirement for ages 0 to 3 years and deferring pediatric studies for ages 3 years to 12 years for this application

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314 81 These commitments are listed below

1 Deferred pediatric studies under PREA for the treatment of travelers' diarrhea in pediatric patients ages 3 years to 12 years

Final Report Submission May 1, 2009

Submit final study reports to this NDA For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product Submit all proposed materials in draft or mock-up form, not final print Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available

We have not completed validation of the regulatory methods However, we expect your continued cooperation to resolve any problems that may be identified

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314 80 and 314 81)

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA New molecular entities and important new biologics qualify for inclusion for three years after approval Your firm is eligible to receive copies of reports for this product To participate in the program, please see the enrollment instructions and program description details at www fda gov/medwatch/report/mmp htm.

If you have any questions, call Andrei Nabakowski, Pharm D , Regulatory Project Manager, at (301) 827-2127

Sincerely,

{See appended electronic signature page}

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

Enclosures(2) Xifaxan™ Package Insert
Xifaxan™ Patient Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-361

APPROVABLE LETTER(S)

10/25/02 AE letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-361

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

Dear Mr Kashiwase

Please refer to your new drug application (NDA) dated December 21, 2001, received December 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rifaximin tablets

We acknowledge receipt of your submissions dated

January 18, 2002
January 22, 2002
February 5, 2002
April 2, 2002
April 3, 2002
April 18, 2002
April 19, 2002
April 22, 2002
April 23, 2002
May 7, 2002
May 9, 2002
May 13, 2002
May 20, 2002
May 30, 2002
June 3, 2002
June 6, 2002
July 2, 2002
July 15, 2002
July 16, 2002
July 19, 2002
July 22, 2002
July 24, 2002
August 5, 2002
August 14, 2002
September 16, 2002

We have completed our review of this application, as amended, and it is approvable Before the application may be approved, however, it will be necessary for you to address the following

1 The single phase III study that evaluated the proposed rifaximin dosage regimen of 200 mg po tid does not provide sufficient evidence to support the approval of rifaximin for the treatment of traveler's diarrhea In order to address this deficiency, you must submit a second adequate and well-controlled clinical trial using the 200 mg po tid regimen that confirms the clinical efficacy demonstrated in Study RFID9801 Specifically, you must demonstrate a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens

3 We find that there are insufficient pharmacokinetic data to assess the level of systemic absorption of rifaximin in patients with traveler's diarrhea You must determine the extent of systemic absorption of rifaximin after oral administration of the proposed dosing regimen to patients with traveler's diarrhea We recommend that you determine this by obtaining full rifaximin pharmacokinetic profiles in a subset of patients

4 You have provided data from an in vitro hepatocyte induction model demonstrating that rifaximin induces cytochrome p450 3A4 (CYP3A4) Therefore, you must obtain information to characterize pharmacokinetic drug-drug interactions between rifaximin and other CYP3A4 substrates that undergo significant presystemic intestinal metabolism, notably oral contraceptives If, in addressing this issue, you plan to conduct additional studies, we strongly recommend that you discuss the protocols for such studies with the Division prior to study initiation

5 Provide details on all drug product lots used in Phase 3 clinical trials, identifying the drug substance lots used in these product lots and providing detailed particle size distribution data for these drug substance lots Based on these data, propose an appropriate acceptance criterion for drug substance particle size distribution

6 Identify those impurities that are degradants in the drug product In the drug product specification, include separate acceptance criteria for identified individual degradants, any unspecified degradant, and total degradants These degradant levels should be monitored during stability studies

7 The submitted stability data in your submissions are not sufficient to assign an expiration date for the product packaged in all proposed market packaging Please provide additional stability data for the drug product, packaged in all intended commercial container/closure systems, and produced at the facility

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314 50(d)(5)(vi)(b) The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level

1 Describe in detail any significant changes or findings in the safety profile

2 When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission
- Present tabulations of the new safety data combined with the original NDA data
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above
- For indications other than the proposed indication, provide separate tables for the frequencies of

adverse events occurring in clinical trials

3 Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies Describe any new trends or patterns identified

4 Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event In addition, provide narrative summaries for serious adverse events

5 Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data

6 Provide a summary of worldwide experience on the safety of rifaximin Include an updated estimate of use for rifaximin marketed in other countries

7 Provide English translations of current approved foreign labeling not previously submitted

In addition, it will be necessary for you to submit draft labeling revised to reflect additional safety and efficacy data submitted

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314 110 If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314 65 Any amendment should respond to all the deficiencies listed We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed

The drug product may not be legally marketed until you have been notified in writing that the application is approved

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Mark Goldberger
10/25/02 09 55 26 AM