CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-554

CHEMISTRY REVIEW(S)

NDA/ANDA 22-554

XIFAXIN® (rifaximin) tablets

Salix Pharmaceuticals, Inc.

David B. Lewis, Ph. D.
ONDQA Division IV, Branch VIII
And
Division of Gastroenterology Products, HFD-180

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Chemistry Review Data Sheet

1. NDA 22-554

2. CMC Review # 1

3. REVIEW DATE: 01-MAR-2010

4. David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-361 (original)	21-DEC-2001
NDA 21-361 CMC review # 1	09-SEP-2002
NDA 21-361 CMC review # 3	13-MAY-2004 (AP)
NDA 21-361/S-007 CMC review	20-MAY-2007 (AP)
NDA 21-361/S-008 CMC review # 2	03-MAR-2009 (AP)
NDA 21-361/S-010 (re-classified as NDA 22-554)	24-JUNE-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-554	24-JUNE-2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Salix Pharmaceuticals, Inc.
Address:	1700 Perimeter Park Drive, Morrisville, NC 27560
Representative:	David Dobrowski, Director Regulatory Affairs
Telephone:	(919) 862-1047

8. XIFAXAN® (rifaximin) tablets

a) XIFAXAN®
b) Rifaximin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 6 NDA (new indication, new clinical division)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION:

This application was initially submitted as an efficacy supplement NDA 21-361/S-010. However, since the new indication was to be reviewed by a different clinical division (HFD-180), the application was re-classified as a Type 6 NDA, and assigned a new NDA number, 22-554.

10. PHARMACOL. CATEGORY: indicated for the maintenance of remission of hepatic encephalopathy in patients 18 years of age of older; this NDA was originally submitted as an efficacy supplement to NDA 21-361, proposing a new indication.

11. DOSAGE FORM: Solid oral tablet

12. STRENGTH/POTENCY: 550 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

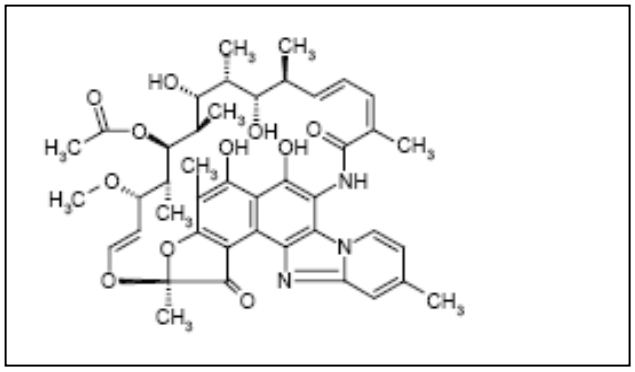
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug substance is Rifaximin (USAN,INN)
CAS Number is 80621-81-4
(2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-e]pyridol[1,2-α]benzimidazole-1,15(2H)-dione,25-acetate

Structure:



Molecular formula is $C_{43}H_{51}N_3O_{11}$
Molecular weight is 785.89 grams per mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	rifaximin	3	adequate	3-02-2009	Adequate for NDA 21-361 S-008
			rifaximin	3	adequate	3-09-2007	Adequate for NDA 21-361 S-007
			(b) (4)	7	adequate		Found adequate to support original NDA 21-361

Note: a variety of Type III packaging DMF's were provided in the application; however, it was noted that the container closure system for the new strength tablet is the same as that for the approved 200-mg tablet. Since this application is being reviewed from the standpoint of CMC as if it were a post-approval supplement, these packaging DMF's were neither reviewed nor noted in the table for section 17.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: none

18. STATUS:

While this review is conducted on a new NDA template, from the standpoint of CMC, this is a post-approval supplement. For regulatory purposes, this has been classified as a Type 6 NDA, and was assigned a new NDA number.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	12-09-2009	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	ACCEPTABLE		Contained within this review
OPDRA	N/A		
EA	ACCEPTABLE	01-MAR-2010	D. Lewis
Microbiology	N/A		Separate OND review

The applicant claimed a categorical exclusion from the requirements to prepare an environmental assessment per 21 CFR 25.31(b), stating that, while action of this application will increase the use of the active moiety (Rifaximin), the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below 1 ppb. A calculation is provided, in which the average number of batches of both the approved 200-mg tablets and the proposed 550-mg tablets will be manufactured through the year (b) (4) The predicted EIC is below 1 ppb.

The Chemistry Review for NDA 22-554

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from the standpoint of CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None (from the standpoint of CMC, this application is a post-approval supplement). No Phase 4 commitments are applicable to the approval of this submission.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance: the drug substance, rifaximin is manufactured and provided from two sources, (b) (4) All CMC information on the drug substance from either source is referred to approved NDA 21-361 and to DMF's (b) (4) and (b) (4) These DMF's were reviewed in support of NDA 21-361 and found adequate to support the NDA for the drug substance. Neither DMF has been updated since the last adequate review, and may be considered to remain adequate to support this NDA 22-554. Although the two manufacturing facilities for Rifaximin were unchanged from those approved for NDA 21-361, they were re-submitted to the Office of Compliance since this submission was re-classified from an NDA 21-361 efficacy supplement to NDA 22-554 Type 6 NDA. According to the Office of Compliance, the two drug substance manufacturing facilities remain acceptable from the standpoint of c-GMP's. All physicochemical information regarding the drug substance is referred to approved NDA 21-361, and to adequate DMF's (b) (4) and (b) (4). DMF (b) (4) was reviewed in March of 2009, in order to evaluate manufacturing changes reported for NDA 21-361, and was found adequate. DMF (b) (4) was reviewed in order to qualify (b) (4) as a drug substance manufacturer for NDA 21-361/S-008, and was also found adequate (March of 2007).

Drug product: the drug product is an oral immediate-release tablet formulated to provide 550 mg of the drug substance, Rifaximin. The tablet is 1 gram in size, and is a (b) (4) tablet with a film coat. The NDA 22-554 drug product is a larger higher-dose version of the approved 200-mg Rifaximin tablets approved in NDA 21-361. The higher-dose tablets are dose-proportional; in fact, (b) (4) is identical

to that which was approved for NDA 21-361. The manufacturing process for the 550-mg tablets differs only in the (b) (4) . The inactive ingredients contained within the 550-mg drug product are identical to those contained within the 200-mg product, and are sodium starch glycolate, glyceryl distearate, colloidal silicon dioxide, microcrystalline cellulose, and talc. The film coat for the tablet is manufactured using the proprietary blend (b) (4) The manufacturing process for the blend, as well as all of the inactive ingredients were reviewed and approved for NDA 21-361, and remain adequate for this NDA. Likewise, the coating ingredient (b) (4) was reviewed and found adequate as a non-compendial excipient for the NDA 21-361 drug product via DMF (b) (4) the facilities used for the manufacture, packaging, and testing of the drug product are unchanged from those approved for NDA 21-361; these facilities were re-submitted to the Office of Compliance for c-GMP evaluation due to the new NDA number (Type 6 NDA). The Office of Compliance recommended that all of the drug product facilities were ADEQUATE to support this NDA (EER Summary report dated 12-07-2009, attached to the end of this review).

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for oral administration with a recommended dose of 1,100 mg daily (one 550-mg tablets twice a day). This is easily available with the dosage unit (550-mg tablet). The 550-mg tablets are packaged in 60-count bottles, 60-count unit-dose in cartons, and 6-count bottles as physician (professional) samples.

The applicant provided 18 months of long-term stability plus 6 months of accelerated stability for three (3) batches of the 550-mg tablets. Data was provided for each presentation (6-ct physician sample, 60-ct commercial bottles, and commercial unit-dose). The applicant also provided statistical analysis for all quantitative attributes, and proposed implementation of a 36-month expiry, which matches that used for the approved 200-mg tablets. Since the 550-mg tablets and the 200-mg tablets are manufactured from a common blend, and since the stability data for the 500-mg tablets exhibited practically no change under any condition, the 36-month expiry is acceptable for the 550-mg tablets. It is noted that the usual data requirement for a new NDA is not as relevant as the usual dataset for a post-approval supplement (from the standpoint of CMC, this is a post-approval supplement). The applicant did perform statistical analysis of all quantitative attributes, for which expiration dating periods of (b) (4) were predicted. Recommended storage conditions are room temperature (25ºC, as defined within the current USP).

The 550-mg tablets are proposed for twice daily dosing; 1 tablet b.i.d, corresponding to 1100 mg per day).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for APPROVAL from the standpoint of CMC due to:

- Acceptable EER status of facilities
- Adequate information regarding manufacture
- Acceptable values for exhibit batches
- Adequate status of referenced DMF's for drug substance
- Identical container closure system for the 550-mg tablets
- Successful method validation for the 550-mg tablet analytical methods
- Suitable justification of specifications
- Adequate stability data on three batches packaged in all proposed presentations; this stability data included statistical analysis. It is noted that the 550-mg tablets are compressed from the same blend as the approved 200-mg tablets
- Adequate labeling sections (dosage forms and strengths, Description section, and How Supplied)

III. Administrative

A. Reviewer's Signature

David B. Lewis, ONDQA Division IV, Branch VIII, primary reviewer
Hasmukh B. Patel, ONDQA Divison IV Branch VIII Chief

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

HFD-180 Division file for NDA 22-554

48 pp withheld in full as (b)(4) CCI/TS immediately after this page .

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

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

/s/

DAVID B LEWIS
03/01/2010
Recommend APPROVAL from the standpoint of CMC.

HASMUKH B PATEL
03/01/2010