CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-554

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH
Subject	Division (Deputy) Director Summary Review
NDA/Supplement #	NDA # 21-554
Applicant Name	Salix Pharmaceuticals, Inc.
Date of Submission	June 24, 2009
PDUFA Goal Date	March 24, 2010
Proprietary Name / Established (USAN) Name	Xifaxan® (rifaximin) tablets
Dosage Forms / Strength	550 mg
Proposed Indication(s)	Maintenance of Remission of Hepatic Encephalopathy in patients 18 years and older.
Action/Recommended Action:	*Approval- Indicated for reducing the risk of overt hepatic encephalopathy recurrence in patients 18 years and older.*

1. Introduction

Rifaximin is currently approved for the treatment of traveler's diarrhea 200 mg three times per day for 3 days in patients ≥ 12 years of age (2004; NDA 21-361). In the current application, NDA 22-554, the sponsor is pursuing the use of rifaximin 550 mg twice daily for maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age. The 200 mg tablet approved under the parent NDA 21-361 and a new NDA number (22-554) was granted to the current supplement due to system migration to DARRTS (Type 6 submission).

This drug obtained orphan status in February 10, 1998 for the treatment of hepatic encephalopathy. At that time it was estimated that 100,000 patients were affected by the disease in the United States.

2. Background

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV. The mechanism of action is to inhibit the DNA-dependent RNA polymerase of the target microorganisms, resulting in inhibition of bacteria protein synthesis. Rifaximin is very poorly absorbed from the intestine, and is felt to act locally on the intestinal microbial flora. It is hypothesized that this action effects ammonia absorption from the intestine. Systemic ammonia is thought to contribute to the neurologic syndrome of hepatic encephalopathy. This occurs in patients who have hepatic dysfunction and are not able to detoxify the ammonia in the portal circulation.

"Hepatic encephalopathy is manifested as a continuum of mental status deterioration, psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and coma. Changes may be observed in personality, consciousness, behavior, and neuromuscular function. Neuromotor signs may include hyperreflexia, rigidity, myoclonus, and asterixis (a coarse, myoclonic "flapping" muscle tremor). The clinical diagnosis of overt HE in subjects with advanced liver disease and portal-systemic shunting is based on two concurrent types of symptoms: impaired mental status (as generally defined by Conn Score) and symptoms of impaired neuromotor functioning (asterixis)."

"The etiology and pathogenesis of hepatic encephalopathy are not known. The main tenet for the pathogenesis of HE is that nitrogenous substances derived from endogenous bacterial metabolism in the GI tract adversely affect brain function. Compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. Once in brain tissue, the compounds produce alterations of neurotransmission that affect consciousness and behavior. Other gut derived neurotoxins have also been implicated. Some of these neurotoxins also accumulate and alter CNS function and include mercaptans, phenols, manganese, short chain fatty acids, bilirubin, and a variety of neuroactive medications."

This application presents one randomized double blind placebo controlled (add-on) study for the maintenance of remission (RFHE3001) of 6 months duration, and a

continuation study (RFHE3002) in which patients have been treated up to 2 years. In addition several clinical pharmacology studies were submitted in this application.

For the proposed indication, the target patient population has a varying degree of hepatic impairment, which could lead to increased systemic exposure of rifaximin. In support of the proposed indication, the sponsor submitted three in vivo and two in vitro clinical pharmacology related studies. The three in vivo studies are (1) Study RFPK1007 to characterize single dose and multiple dose pharmacokinetics and to evaluate food effect in healthy subjects, (2) Study RFPK1008 to assess drug interaction with midazolam in healthy volunteers, and (3) Study RFHE3002PK to determine the effect of different degrees of hepatic impairment on the pharmacokinetics of rifaximin. The two in vitro studies were conducted to evaluate if rifaximin is a substrate and/or inhibitor of efflux transporter(s) and to evaluate protein binding in blood samples from PK studies. The sponsor also submitted the final study report of RFPK1002 titled "A two-way crossover scintigraphic evaluation of the disintegration of two batches or rifaximin" and used it to support twice daily dosing frequency. The RFPK1002 is considered only supportive as it was a comparative study for 200 mg tablets.

Several issues were raised by this application and are discussed throughout this memo:

- Efficacy was based on a single phase 3 study
- Adequacy of the primary endpoint definition and assessment methodology to evaluate hepatic encephalopathy (HE)
- Safety of proposed dose in patients with severely impaired hepatic function
- Long-term use of rifaximin and the potential for change in the gut flora and the development of resistance.

A Gastroenterology Advisory Committee meeting was held on February 23, 2010.

Overall Summary:
In summary, the review team as well as the Advisory Committee recommends approval of this application based upon the fact that study RFHE3001 demonstrated substantial evidence of efficacy and for the majority of patients, and it appeared to be safe in this population.

Outstanding issues were recommended for study post-marketing: additional studies in patients with severe hepatic insufficiency (Child-Pugh class C, MELD >19 and MELD $\geq$ 25) to collect additional safety data; pharmacokinetic studies in patients with severe renal and hepatic impairment; further study on p-glycoprotein transporter inhibitors, chronic non-clinical toxicology with exposure to high levels of rifaximin, a study of efficacy of rifaximin as monotherapy; collect additional ECG data in treated patients.

These studies are appropriate for post marketing because what is known about the rifamycin class of drugs gives us some assurance of the safety of long term use regarding toxicity and resistance. The risk is low, but it needs to be documented, especially as the numbers of patients with hepatic insufficiency increase in the general population due to Hepatitis C. Finally, while the AUCs in patients with Child-Pugh

class A, B, and C are increased when compared to healthy volunteers, the absolute concentration is very low. Again, there is no data in patients with the most severe grade of liver insufficiency (MELD ≥ 25). These facts are outlined in the labeling and will be amended as more information is available as a result of these studies.

Finally, this is a serious life threatening condition and an unmet medical need in an orphan population. For these reasons as well as those outlined in this review, the benefit risk is considered favorable for approval.

I agree with the Advisory Committee majority recommendations to approve rifaximin to decrease the risk of overt hepatic encephalopathy recurrence in patients ≥ 18 years of age. (b) (4) 91% of patients were taking concomitant lacutlose, and that patients with the most severe hepatic insufficiency were not studied. The label will contain a new entry under Warnings and Precautions regarding use in patients with severe hepatic impairment (Child-Pugh C).

3. CMC

The CMC review recommended that "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)

"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 2014. The predicted EIC is below 1 ppb."

"I concur with the conclusions reached by the chemistry reviewer. There are no outstanding issues."

4. Nonclinical Pharmacology/Toxicology

The following information was placed in the label as a result of this review.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Malignant schwannomas in the heart were significantly increased in male Crl:CD® (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg/day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for travelers' diarrhea, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for hepatic encephalopathy, based on relative body surface area comparisons). There was no increase in tumors in Tg.rasH2 mice dosed orally with rifaximin for 26 weeks at 150 to 2000 mg/kg/day (doses equivalent to 1.2 to 16 times the recommended daily dose for travelers' diarrhea and equivalent to 0.7 to 9 times the recommended daily dose for hepatic encephalopathy, based on relative body surface area comparisons).

Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA synthesis assay, or the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose of 600 mg/day, and approximately 2.6 times the clinical dose of 1100 mg/day, adjusted for body surface area).

Animal Toxicology and/or Pharmacology

Oral administration of rifaximin for 3-6 months produced hepatic proliferation of connective tissue in rats (50 mg/kg/day) and fatty degeneration of liver in dogs (100 mg/kg/day). However, plasma drug levels were not measured in these studies. Subsequently, rifaximin was studied at doses as high as 300 mg/kg/day in rats for 6 months and 1000 mg/kg/day in dogs for 9 months, and no signs of hepatotoxicity were observed. The maximum plasma AUC0-8 hr values from the 6 month rat and 9 month dog toxicity studies (range: 42-127 ng•h/mL) was lower than the maximum plasma AUC0-8 hr values in cirrhotic patients (range: 19-306 ng•h/mL).

In their review the non-clinical reviewers had the following comments and recommendations regarding this issue. "The incidence of hepatotoxicity in nonclinical studies, albeit inconsistent, raises a safety concern for the intended patient population (i.e., cirrhosis patients with hepatic encephalopathy). This concern is compounded by the results of clinical study RFHE3002PK, which showed an increase in plasma drug levels in cirrhotic patients. At the proposed dose of 550 mg bid, the AUC in cirrhotic patients was 10 to 20-fold higher than that observed in healthy volunteers. The increase in AUC was correlated with severity of hepatic injury, based on Child-Pugh classification. In addition, the range of AUCs in cirrhotic patients, 28-412 ng·hr/ml, is higher than the range of AUCs in animal toxicity studies (42-127 ng·hr/ml). Therefore, the animal toxicity studies do not provide assurance of safety for rifaximin use in cirrhotic patients, particularly for those with more severe hepatic injury. The increased systemic exposure in cirrhotic patients is a cause for concern, given the limited absorption of rifaximin in animals and humans with normal liver function, the incidence of liver injury in toxicity studies that lacked toxicokinetic data, and the limited information about systemic toxicity. Furthermore, it will be difficult to monitor for rifaximin-induced liver injury in cirrhotic patients."

"In order to address the safety concern about higher AUC values in cirrhotic patients, the Sponsor must conduct a chronic oral toxicology study that evaluates plasma AUC exposure in animals that is comparable to the highest plasma AUCs observed in cirrhotic patients (approximately 400 ng·hr/ml). These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used. The chronic toxicity study that is needed to address the safety concern about increased AUC values in cirrhotic patients may be conducted as a post-marketing study."

The non-clinical reviewers qualified the impurity (b) (4) in their addendum to their original review.

"I concur with the labeling proposals and recommended post-market study made by the pharmacology/toxicology reviewer. There are no outstanding pharmacology/toxicology issues that preclude approval."

5. Clinical Pharmacology/Biopharmaceutics

In general, the amount of rifamixin that is systemically absorbed is small. As described below the systemic levels measured in patients with hepatic impairment are higher than those in normal healthy volunteers, however, the absolute level is present in nanograms. The safety profile seen in the clinical trials did not reveal any hepatic toxicity issues; however, patients with the most severe levels of hepatic impairment were not studied. Given the known information, including clinical and non-clinical, the reviewers recommended labeling and PMR/PMCs to study the efficacy of hepatic impairment in the metabolism and exposure to rifaximin in patients with more severe liver disease.

The reviewers summarized the background well in the following paragraphs:

"Mass balance study report was submitted to NDA 21-361 original submission (please, see clinical pharmacology review by Dr. Kofi Kumi for more details). When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces as the unchanged drug and a small amount (<1% dose) as the metabolite, 25-desacetyl rifaximin. About 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as rifaximin. Rifaximin accounted for about 18% of radioactivity in plasma. Biliary excretion of rifaximin was suggested in a separate study. Rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa. In Caco-2 cell permeability study, the apparent apical to basolateral permeability of rifaximin was comparable to that of mannitol, a low permeability drug."

"Taken together, these results suggest that the oral absorption of rifaximin is limited yet once absorbed rifaximin may undergo extensive metabolism. Of note, the absolute

bioavailability was not evaluated, and the relative contribution of biliary excretion and the enzymes responsible for the metabolism of rifaximin are unknown."

"The proposed target population has a certain degree of hepatic impairment leading to reduced rifaximin metabolism. Therefore, the main clinical pharmacology question for this application has been if the submitted clinical pharmacology and biopharmaceutics information adequately supports safe and effective use of rifaximin in this new patient population."

They further recommend that "if the clinical division found the overall safety and efficacy of rifaximin in the target patient population acceptable, those deficiencies should be addressed through labeling languages and post-marketing commitments".

Key clinical pharmacology results were as follows:

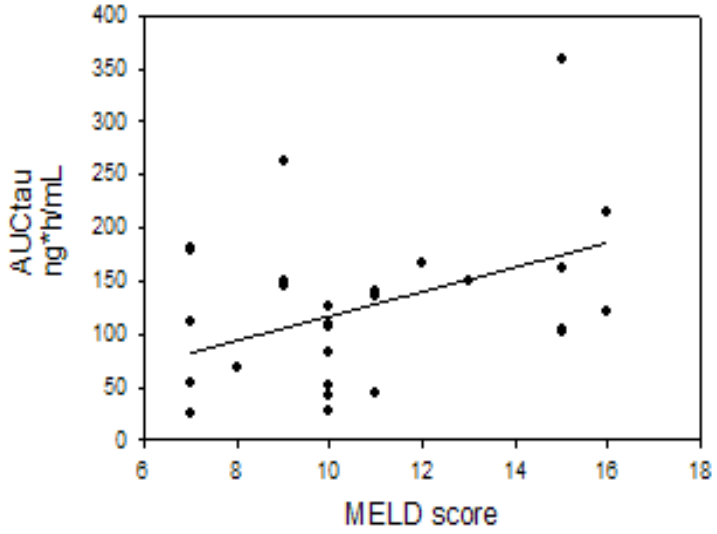
The PK of rifaximin in patients with a history of HE was evaluated after administration of XIFAXAN, 550 mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure (AUCτ) in patients with a history of HE (147 ng•h/mL) was approximately 12-fold higher than that observed in healthy subjects following the same dosing regimen (12.3 ng•h/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUCτ was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects (Table 1). The maximum AUC was 246 ng·h/mL.

Table 1
Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class[1]

	Healthy Subjects (n = 14)	Child-Pugh Class		
		A (n = 18)	B (n = 7)	C (n = 4)
AUC_{tau} (ng•h/mL)	12.3 ± 4.8	118 ± 67.8	161 ± 101	246 ± 120
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.1 ± 12.6	35.5 ± 12.5
T_{max}[2] (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (0.97, 1)	1 (0, 2)

[1] Cross-study comparison with PK parameters in healthy subjects
[2] Median (range)

Figure 1: Systemic Exposure of Rifaximin by MELD Score



Food Effect in Healthy Subjects
A high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC) of rifaximin by 2-fold (Table 2).

Table 2
Mean (± SD) Pharmacokinetic Parameters After Single-Dose Administration of XIFAXAN Tablets 550 mg in Healthy Subjects Under Fasting and Fed Conditions (N = 12)

Parameter	Fasting	Fed
C_{max} (ng/mL)	4.1 ± 1.5	4.8 ± 4.3
T_{max}[1] (h)	0.8 (0.5, 2.1)	1.5 (0.5, 4.1)
Half-Life (h)	1.8 ± 1.4	4.8 ± 1.3
AUC (ng•h/mL)	11.1 ± 4.2	22.5 ± 12

[1]Median (range)

This data shows that XIFAXAN can be administered with or without food.

Distribution
Rifaximin is moderately bound to human plasma proteins. In vivo, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when XIFAXAN 550 mg was administered.

Drug Interactions
An in vitro study suggests that rifaximin is a substrate of P-glycoprotein. In the presence of P-glycoprotein inhibitor verapamil, the efflux ratio of rifaximin was reduced greater than 50% in vitro. The effect of P-glycoprotein inhibition on rifaximin was not evaluated in vivo.

The inhibitory effect of rifaximin on P-gp transporter was observed in an in vitro study. The effect of rifaximin on P-gp transporter was not evaluated in vivo.

Midazolam
After XIFAXAN 550 mg was administered three times a day for 7 days and 14 days to healthy subjects, the mean AUC of single midazolam 2 mg orally was 3.8% and 8.8% lower, respectively, than when midazolam was administered alone. The mean Cmax of midazolam was also decreased by 4-5% when XIFAXAN was administered for 7-14 days prior to midazolam administration. This degree of interaction is not considered clinically meaningful.

The effect of rifaximin on CYP3A4 in patients with impaired liver function who have elevated systemic exposure is not known.

Finally, a thorough QT (TQT) study was not performed in this application or for the traveler's diarrhea indication. According to the CDER DCPR QT Interdisciplinary Review Team; "For drugs with systemic bioavailability, we typically recommend a thorough QT/QTc study. In this case, however, the bioavailability of rifaximin is low in healthy volunteers but increases in patients (mean unbound Cmax- 0.017 μM in Child-Pugh C category). Potent inhibitors of hERG are typically active in the nM range. Rifaximin inhibited hERG expressed in a mammalian cell line quite weakly, with an IC50 greater than 100 μM. Therefore QT liability through hERG inhibition is unlikely." The QT team recommended that ECGs be evaluated in patients with severe liver impairment to look at a potential effect the highest exposure, but no TQT was required.

Comparison of the exposure of rifaximin in patients with hepatic impairment to that seen in other rifamycin products is of interest as these are used chronically and have a known safety profile. The following data is in healthy patients taken from the approved labeling. The Cmax for 600 mg of rifampin given intravenously is 17.4 mcg/mL, for rifapentine 600 mg orally is 15 mcg/mL, and 300 mg of rifabutin is 375 ng/mL (highly lipophilic). Compare these values to the Cmax of rifabutin in Child-Pugh class C patients 35 ng/mL. While the fact that these levels are an order of magnitude higher than that of rifaximin, additional data should be collected post approval, but this data is somewhat reassuring regarding safety.

The clinical pharmacology team recommended PMCs listed in section 12 of this review.

"I concur with the conclusions reached by the clinical pharmacology reviewer regarding labeling and that more information will be obtained through PMR/PMC studies otherwise, there are no outstanding clinical pharmacology issues that preclude approval. The experience from the clinical trials for the safety of rifaximin in this target population is discussed in the safety section and it supports the approval of this indication."

6. Clinical Microbiology

No clinical microbiology was obtained in the pivotal clinical trials. According to the microbiology review: "In the absence of any microbiological data, the long term effects of rifaximin on gut flora and any change in the in vitro susceptibility of gut flora to rifaximin and other antimicrobial drugs within the rifamycin class cannot be evaluated."

"Microorganisms can develop drug resistance during treatment (i.e., under drug pressure), and the same possibility exists with the use of rifaximin. It is important to note, however, that there are several drugs of the rifamycin class (e.g., rifampin, rifabutin, and rifapentine) that are currently approved, marketed and used in combination with other drugs for the long term treatment of tuberculosis. The role of these products on in vitro susceptibility of gut flora, and the additional impact of the long term use of rifaximin on gut flora has not been evaluated."

They recommend the following: "If rifaximin is approved for the treatment of HE, post marketing studies should be considered to evaluate the effect of long term treatment with rifaximin on the gut flora and in vitro susceptibility to rifaximin and other rifamycin antimicrobial drugs, and depending on the outcome of such studies, consideration may need to be given to evaluating the clinical significance of in vitro "resistance" on the efficacy of rifaximin."

I am in agreement. This will be requested as a post marketing study.

7. Clinical/Statistical-Efficacy

The efficacy of rifaximin was demonstrated in one clinical trial of six months duration (RFHE3001). Additional supportive information was obtained in a continuation study which extended the use of rifaximin for two years in an unblinded fashion (RFHE3002). The primary results of the pivotal trial are described below.

The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible subjects had ≥ 2 episodes of HE associated with chronic liver disease in the previous 6 months.

A total of 299 subjects were randomized to receive either XIFAXAN (n=140) or placebo (n=159) in this study. Patients had a mean age of 56 years (range, 21-82 years), 81% < 65 years of age, 61% were male and 86% White. At baseline, 67% of patients had a Conn score of 0 and 68% had an asterixis grade of 0. Patients had MELD scores of either ≤ 10 (27%) or 11 to 18 (64%) at baseline. No patients were enrolled with a MELD score of > 25. Nine percent of the patients were Child-Pugh Class C. Lactulose was concomitantly used by 91% of the patients in each treatment arm of the study. Per the study protocol, patients were withdrawn from the study after experiencing a breakthrough HE episode. Other reasons for early study

discontinuation included: adverse reactions (XIFAXAN 6%; placebo 4%), patient request to withdraw (XIFAXAN 4%; placebo 6%) and other (XIFAXAN 7%; placebo 5%).

The primary endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as a marked deterioration in neurological function and an increase of Conn score to Grade ≥ 2. In patients with a baseline Conn score of 0, a breakthrough overt HE episode was defined as an increase in Conn score of 1 and asterixis grade of 1.

Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in the XIFAXAN group and by 73 of 159 subjects (46%) in the placebo group during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE breakthrough by 58% during the 6-month treatment period based on the Kaplan-Meier event-free curve for all subjects (n = 299) in the study.

When the results were evaluated by the following demographic and baseline characteristics, the treatment effect of XIFAXAN 550 mg in reducing the risk of breakthrough overt HE recurrence was consistent for: sex, baseline Conn score, duration of current remission and diabetes. The differences in treatment effect could not be assessed in the following subpopulations due to small sample size: non-White (n=42), baseline MELD > 19 (n=26), Child-Pugh C (n=31), and those without concomitant lactulose use (n=26).

HE-related hospitalizations (hospitalizations directly resulting from HE, or hospitalizations complicated by HE) were reported for 19 of 140 subjects (14%) and 36 of 159 subjects (23%) in the XIFAXAN and placebo groups respectively. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE-related hospitalizations by 50% during the 6-month treatment period.

The CDTL, MO reviewer and the AC all recommended approval of this application based upon the statistically significant and clinically meaningful results of this study. The consult reviewer from neurology raised several concerns about the design of this study. The first concern was regarding the assessment of the primary endpoint of breakthrough HE. The endpoint relied on the Conn Score which is known not to be sensitive in differentiating milder severities of HE. Also it is somewhat imprecise and depends on clinician judgment. These issues were discussed at the AC and the majority of members acknowledged the issues raised regarding the primary endpoint, and they felt that this was the best study conducted to date in a patient population which is very difficult to study. The statistical reviewer ran several sensitivity tests which confirmed the primary results. Additional information was submitted by the sponsor which further addressed this issue. This information was obtained after completion of the neurology consult. As is noted below, the AC members

recommended that future studies look into more precise endpoints. (for more detail refer to primary reviews, consult and the AC minutes)

There was an additional concern raised by the neurology consultant regarding enrollment. "There is also insufficient evidence that the occurrence, or lack thereof, of episodes of hepatic encephalopathy in the months prior to study entry was accurately recorded, either; an accurate recording of the frequency and severity of such episodes was needed for one of the main inclusion criteria for this study to be fulfilled". The result of this discussion with the AC was its recommendation to use another term rather than remission, because in relying on the Conn Score alone clearly some of the patients were not in absolute remission upon entry into the study. The committee members said that an absolute remission was difficult to have in these patients (Conn Score 0 vs. 1) as the mental status may fluctuate in a day. Overall, the AC members felt that the entry Conn Score was significantly distinct from the breakthrough of overt HE Conn Score, that the overall results were not affected by this difference in baseline characteristic, and that the sponsor followed the protocol.

Finally, this study uses concomitant administration of lactulose in approximately 90% of the patients, which is approved for use in HE. The study design thus demonstrated the superiority of rifaximin compared to a placebo, however, because of the concomitant use of lactulose, the true effect of rifaximin as monotherapy is unknown. There is literature which questions the usefulness of lactulose in these patients, however, this is an old drug, and it appeared to improve mental status in the older studies. Therefore, if one believes that lactulose is active, then rifaximin is an adjunctive therapy. However, the converse is not necessarily true. The AC members recommended and we agree that the Salix should study rifaximin in as monotherapy compared to lactulose and rifaximin in a prospective randomized double-blind study.

Overall I am in agreement with the recommendation for approval based upon the strong results of study RFHE3001 with additional support from study RFHE3002

In conclusion, I agree with the review team and the Advisory Committee members that this study supports approval of rifaximin for reduction in risk of overt hepatic encephalopathy recurrence in patients ≥ 18 years of age.

8. Safety

The data described below reflect exposure to XIFAXAN 550 mg in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of XIFAXAN 550 mg taken two times a day for reducing the risk of overt hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-controlled clinical trial (n = 140) and in a long term follow-up study (n = 280). The population studied had a mean age of 56.26 (range: 21-82) years; approximately 20% of the patients were ≥ 65 years old, 61% were male, 86% were White, and 4% were Black. Ninety-one percent of patients in the trial were taking lactulose concomitantly. All adverse reactions that occurred at an incidence ≥ 5% and at a higher incidence in XIFAXAN 550 mg-treated subjects than in the placebo

group in thee 6-month trial are provided below (These include adverse events that may be attributable to the underlying disease.)

Adverse Reactions Occurring in ≥ 5% of Patients Receiving XIFAXAN and at a Higher Incidence Than Placebo

	Number (%) of Patients	
MedDRA Preferred Term	**XIFAXAN Tablets 550 mg TWICE DAILY N = 140**	**Placebo N = 159**
Edema peripheral	21 (15%)	13 (8%)
Nausea	20 (14%)	21 (13%)
Dizziness	18 (13%)	13 (8%)
Fatigue	17 (12%)	18 (11%)
Ascites	16 (11%)	15 (9%)
Muscle spasms	13 (9%)	11 (7%)
Pruritus	13 (9%)	10 (6%)
Abdominal pain	12 (9%)	13 (8%)
Abdominal distension	11 (8%)	12 (8%)
Anemia	11 (8%)	6 (4%)
Cough	10 (7%)	11 (7%)
Depression	10 (7%)	8 (5%)
Insomnia	10 (7%)	11 (7%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (5%)
Back pain	9 (6%)	10 (6%)
Constipation	9 (6%)	10 (6%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

The following adverse reactions, presented by body system, have also been reported in the placebo-controlled clinical trial in greater than 2% but less than 5% of patients taking XIFAXAN 550 mg taken orally two times a day for hepatic encephalopathy. The following includes adverse events occurring at a greater incidence than placebo, regardless of causal relationship to drug exposure.

Ear and Labyrinth Disorders: Vertigo
Gastrointestinal Disorders: Abdominal pain lower, abdominal tenderness, dry mouth, esophageal variceal bleed, stomach discomfort
General Disorders and Administration Site Conditions: Chest pain, generalized edema, influenza like illness, pain NOS
Infections and Infestations: Cellulitis, pneumonia, rhinitis, upper respiratory tract infection NOS
Injury, Poisoning and Procedural Complications: Contusion, fall, procedural pain
Investigations: Weight increased
Metabolic and Nutritional Disorders: Anorexia, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hyponatremia

Musculoskeletal, Connective Tissue, and Bone Disorders: Myalgia, pain in extremity
Nervous System Disorders: Amnesia, disturbance in attention, hypoathesia, memory impairment, tremor
Psychiatric Disorders: Confusional state
Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis
Vascular Disorders: Hypotension

The most frequent SAEs (serious adverse events) (i.e., experienced by ≥ 5 subjects total) were hepatic cirrhosis (in 3 rifaximin, 6 placebo subjects), ascites (in 4 rifaximin, 3 placebo subjects), esophageal varices hemorrhage (in 4 rifaximin, 2 placebo subjects), acute renal failure (in 2 rifaximin, 4 placebo subjects), and pneumonia (in 4 rifaximin, 1 placebo subjects), excluding HE episodes that were SAEs due to hospitalization. Of the 43 subjects who experienced the most frequent SAEs, only 6 were Child-Pugh A and 37 were Child- Pugh B or C. The frequent SAEs occurred at comparable rates between rifaximin and placebo groups, although rifaximin subjects had higher rates of esophageal varices (3.1% rifaximin, versus 1.4% placebo) and pneumonia (3.1% rifaximin, versus 0.7% placebo) in RFHE3001. There were two patients in RFHE3001 who developed C. difficile colitis and three in RFHE3002. No placebo patients developed C. difficile colitis.

It is expected that patients taking antibiotics are at increased risk for C. difficile colitis. This fact is already in the label under warnings and precautions for traveler's diarrhea. This would also apply to its use in HE patients.

The medical reviewer had the following comments regarding pneumonia. "Pneumonia is common in cirrhotic patients in both the hospital and community settings. The incidence of community acquired pneumonia has been shown to range between 7% and 23% in cirrhotic patients. In study RFHE3001, pneumonia SAEs were experienced by 4 rifaximin treated subjects (3.1%) and 1 placebo-treated subject (1.4%). In review of SAE reports of pneumonia, the subjects had several predisposing risk factors for pneumonia, including the following: chronic liver disease, alcoholism, hepatitis C, hepatic hydrothorax, chronic obstructive pulmonary disease, portal hypertension, diabetes mellitus, and smoking."

"The incidence of community acquired pneumonia has been shown to range between 7% and 23% in cirrhotic patients. In the RCT Study population; pneumonia was experienced by 4 subjects in the rifaximin group (2.9%) versus 1 subject in the placebo group (0.6%). In the Long Term Rifaximin Experience population, pneumonia was experienced by12 subjects (3.6%), and lobar pneumonia by 4 subjects (1.2%) for a total of 16 subjects (4.8%) with pneumonia. An additional 7 subjects developed pleural effusion. While the increased incidence of pneumonia in the rifaximin group compared to the placebo group is concerning, it is difficult to draw firm conclusions about the risk in this population already at high risk for these complications."

"During RFHE3001 plus RFHE3002 experience, 5 subjects in the placebo crossover group and 1 subject in the rifaximin rollover group experienced pneumonia SAEs.

Pneumonia SAE event rates were similar between the RFHE3001 rifaximin group (0.13 events/PEY) and the placebo crossover/rifaximin rollover groups (0.13 events/PEY)."

Another important safety consideration is outlined as follows by the medical officer. "The incidence of treatment-emergent adverse events (TEAE) increased as the liver function worsened. Nonetheless, the incidence of TEAE increased with decline in liver function in placebo groups as well, and the TEAE rate was similar between rifaximin treatment group and placebo group among patients with the same Child-Pugh Class liver function, except deaths which was numerically higher in the rifaximin arm. Based on the current information, there is no obvious correlation with the degree of liver impairment and incidence of adverse event. It should be noted that relatively limited safety data are available for patients with severe liver impairment in this NDA."

Review of the ISS (Integrated Summary of Safety) from studies conducted for the treatment of HE and IBS did not reveal any additional safety issues. For detailed information regarding safety refer to Medical Officer Review.

The safety reviewer from Office of Surveillance and Epidemiology reviewed the AERS safety data base and did not uncover any new safety signals.

As a result of these reviews as well as discussion at the AC, rifaximin was deemed safe for use in this population. However, it is unknown what the toxicity profile may be in patients with the most severe level of hepatic insufficiency as they were not studied. This is noted in the indication section of the label. In addition, the labeling carries a new Warning and Precaution regarding this potential issue (5.4 Severe (Child-Pugh C) Hepatic Impairment).

In conclusion, I agree with the review team that there are no new safety concerns raised by this new data. PMR studies for safety are outlined below.

9. Advisory Committee Meeting

This product was discussed at the Gastroenterology Advisory Committee on February 23, 2010.

The following questions were asked of the committee and the votes are recorded below.

1. (Discussion Question)
Study RFHE3001 enrolled a patient population with hepatic encephalopathy (HE). To be eligible patients had to have a history within the past 6 months prior to screening of ≥ 2 episodes of overt HE defined as Conn score ≥ 2. At enrollment the patients were required to have Conn scores of 0 or 1. At least 1 of the prior episodes must have been verifiable from medical records. Hepatic encephalopathy episodes primarily attributed to GI

hemorrhage requiring ≥ 2 units of blood, medications (e.g., narcotics), renal failure requiring dialysis, or CNS insult were not counted as a prior, qualifying episode of HE. Two thirds of patients in the trial had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. Ninety one percent of patients were taking lactulose.

How should remission be defined in overt episodic HE? Should patients with a Conn score of 1 be considered to be in remission?

Committee members expressed that it is difficult to define, describe, and assign a specific Conn Score to a patient at any one specific time; mental status fluctuations are observed over the course of a day or from day to day. Although, the Conn index is a simple and reasonably valid measure, however, the issue lies in that it may not be adequate to address the syndrome over time and to properly assess a patient. The committee unanimously agreed that a Conn Score of 1 is not remission, based on the true definition of remission. It is difficult to assess stability when a patient's mental status may be fluctuating between scores on a given day.

2. (Discussion Question)
For future clinical trials, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints), and how should they be measured for:

- decreasing the risk of episodes of overt HE
- treatment of overt HE

Committee members commented that there is a need to:

- *Better capture uniform assessment of endpoints through the use of blinded, independent reviewers;*
- *Obtain mean cumulative frequency of episodes of HE as an endpoint to obtain assessment of effect over time;*
- *Consider time to first hospitalization as an endpoint;*
- *Perform repeated measure analysis by measuring Conn score at specific points in time during treatment;*
- *Utilize neuro-imaging techniques;*
- *Utilize more sensitive neuro-psych testing in addition to the Conn score, including counts of Asterixis frequency.*

3. **(Voting Question)**
Do the clinical data included in the rifaximin application provide substantial evidence of efficacy for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)?
Responses: Yes: 15 No: 3* Abstain: 0
** a panel member placed a vote in the electronic voting system as "YES; however, the panel member verbally stated his vote as "No".*

In your response, please discuss your thinking regarding the following issues:

- Which clinical data, if any, provide substantial evidence of efficacy?
- What, if any, are the deficiencies in the clinical data that make the evidence less than substantial?

The committee members who voted "Yes" expressed that the pivotal trial's primary and secondary endpoints showed consistency of findings. The consensus among the committee members was that the drug labeling needs to include information that rifaximin is to be used as an adjunct to lactulose. The committee voiced their opinion that clinical data deficiencies were related to the lack of use of MELD score measurement during the trial. They also expressed that they felt that patients with a MELD score greater than 25 should have been evaluated.

The committee members who voted "No" felt that the single study data was strong, but not compelling and that a second confirmatory study should have been conducted. There were concerns raised because of lack of clinical efficacy data for use of the product as a single agent, without accompanying use of lactulose. These members also were concerned that while the drug may have demonstrated maintenance of remission, it did not demonstrate remission because patients were not all in remission when they entered the trial. It was also suggested that the efficacy of the drug should be demonstrated patients not using lactulose.

4. **(Voting Question)**
Has the safety of rifaximin at the proposed dose and duration been adequately assessed? In answering this question please discuss whether additional analyses or trials are needed.
Responses: Yes: 12 No: 6 Abstain: 0

A majority of committee members commented that the safety of rifaximin has been adequately addressed. For those that voted "NO", the concern raise was relate to the 3espect long term use of the drug, the effects of the drug on the gut flora, and the unanswered questions regarding the cardiovascular effects (QT) of the drug.
Panel members recommended that the Agency consider

- *The conduct of additional studies in during post-marketing*
- *Further evaluation of patients with more serious liver disease, Mel score greater than 25*
- *Long term effects on gut flora changing with use*
- *Development of drug resistant organisms with use*
- *Surveillance regarding C. difficile*
- *Additional monitoring of ECGs.*

5. **(Voting Question)**
Is the safety of rifaximin at the proposed dose and duration acceptable?
Responses: Yes : 13 No: 5* Abstain: 0
** a panel member placed a vote in the electronic voting system as "YES; however, the panel member verbally stated his vote as "No".*

In general it was felt to be safe. The majority of the committee members stressed the need for surveillance of infection as with drug resistant organisms in phase 4 studies of long duration. There was interest in obtaining additional information in patients with more severe hepatic impairment post-marketing. (see transcript for more detail)

6. **(Voting Question)**

In light of the safety and efficacy data presented in this application, does the risk benefit profile support approval of rifaximin for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)?
Responses: Yes: 14 No: 4 Abstain: 0

The committee commented and recommended:

- *A need to conduct Phase IV post-marketing studies;*
- *The conduct of further studies: on patients with MELD score of 25 or greater (the most ill patients) and for a longer duration;*
- *Labeling to reflect concomitant use with lactulose and suggested use only in patients with Childs Class A and B, MELD score less than 25;*
- *The clinical data supports the demonstration of significant improvement in patients with HE but does not support a finding of remission in patients with HE.*

10. Other Relevant Regulatory Issues

- **PREA** requirements do not apply as this drug was granted orphan designation.
- ***DSI Audits:*** *Five sites were inspected in support of this NDA. Although minor issues were noted at Dr. Poordad's and Dr. Gorbakov's sites, the findings are unlikely to impact data integrity. The data from the 5 sites are acceptable in support of the NDA.*
- ***Financial Disclosure:*** *provided and acceptable.*
- ***Other consults:***

SEALD provided comments to labeling which were discussed with the review team and the final agreements have been made to the final draft labeling

Division of Drug Marketing, Advertising, and Communications (DDMAC)
DDMAC provided comments to draft labeling for consideration by DGP.

During team review meetings (including DDMAC) and in discussions of the labeling during final negotiations comments sent to the division from DDMAC were discussed, and the final approved labeling reflects the agreements reached in these negotiations.

There are no other unresolved relevant regulatory issues

11. Labeling

- Physician labeling: the labeling for 200 mg tablets and 550 mg tablets are included in the same labeling. Each section refers to either traveler's diarrhea or HE. This was done to prevent the use of either tablet for the opposite indication. It was felt that having all this information in one label would prevent that from occurring.
- Patient labeling: changes were made and agreed upon with the applicant to reflect the changes made in the Physician labeling.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend approval of this NDA with the agreed upon labeling changes.

- Risk Benefit Assessment: As described above the benefit risk for this indication is favorable.

- Recommendation for Post-marketing Risk Management Activities: None needed beyond labeling

- Recommendation for other Postmarketing Study Requirements/Commitments: PMR/PMCs will be required/requested as listed below.

PMRs are as follows:

1615-1 A chronic oral nonclinical toxicology study that evaluates AUC exposure in animals that is comparable to the highest AUCs observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

1615-2 A randomized, controlled clinical trial to evaluate the safety of rifaximin in patients with hepatic encephalopathy classified as Child-Pugh C, MELD > 19, and MELD ≥ 25 hepatic impairment.

1615-3 A pharmacokinetic trial in patients with severe hepatic impairment (MELD 19 - 25 and MELD > 25). This may be performed as a sub study in the ongoing Phase 3 trial ((b) (4) , "A multicenter, open label trial to evaluate the long term safety and tolerability of rifaximin 550 mg BID in subjects with a history of hepatic encephalopathy"), or as part of the required clinical trial described under PMR 1615-2.

1615-4 A pharmacokinetic trial in patients with concurrent renal insufficiency and liver impairment to determine the extent of elevation of systemic exposure of rifaximin which may lead to worsening of hepatic function. The PK data should be collected and analyzed by the degree of renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score. A population PK approach will be acceptable.

1615-5 A randomized controlled trial to evaluate the effect of long term rifaximin treatment on the gut flora. In vitro susceptibility testing to rifaximin and other antimicrobial drugs must be included.

The Following PMCs were agreed upon by the applicant:

1615-6 A randomized, controlled clinical trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt hepatic encephalopathy.

1615-7 An in vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) of rifaximin pharmacokinetics in healthy subjects.

1615-8 An in vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter.

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	L. Dimick
Medical Team Leader Review (CDTL)	H. Gallo-Torres
Statistical Review	B. Vali
Pharmacology Toxicology	N. Mehta
CDER DCPR QT Interdisciplinary Review Team	N. Stockbridge
Neurology Consult	R. Mani
CMC Review	D. Lewis
Clinical Pharmacology Review	I. Kim
Microbiology Reviewer	A. Purfield
Division of Scientific Investigations	K. Malek
OSE/DVP	A. Corken-Mackey
SEALD labeling comments	
OSE/DRISK	K. Klemm, C. Miller

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DRISK=Division of Risk Management
DDMAC= Division of Drug Marketing, Advertising, and Communications
CDTL=Cross-Discipline Team Leader
DVP = Division of Pharmacovigilance

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/

JOYCE A KORVICK
03/24/2010