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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) Tablets
Initial U.S. Approval: 2004

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN Tablets and other antibacterial drugs, XIFAXAN Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

----------INDICATIONS AND USAGE----------

XIFAXAN Tablets are a rifamycin antibacterial indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Travelers' diarrhea: one 200 mg tablet taken orally three times a day for 3 days (2.1)
- XIFAXAN Tablets can be taken with or without food (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg tablets (3)

----------CONTRAINDICATIONS----------

- History of hypersensitivity to rifaximin, or to rifamycin antimicrobial agents, or any of the components of XIFAXAN Tablets (4.1)

----------WARNINGS AND PRECAUTIONS----------

- Travelers' Diarrhea Not Caused by *E. coli*: XIFAXAN Tablets were not found effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue treatment with XIFAXAN (5.1)
- *Clostridium difficile*-Associated Diarrhea: evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5%) were flatulence, headache, abdominal pain, rectal tenesumus, defecation urgency and nausea (6.1)

To report suspected adverse reactions, contact Salix Pharmaceuticals at 1-866-669-7597 and www.Salix.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xxx/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN Tablets and other antibacterial drugs, XIFAXAN Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Travelers' Diarrhea

XIFAXAN® Tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* [see *Warnings and Precautions (5)*, *Clinical Pharmacology (12.4)* and *Clinical Studies (14.1)*].

1.2 Limitations of Use – Travelers' Diarrhea

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*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Travelers' Diarrhea:

The recommended dose of XIFAXAN Tablets is one 200 mg tablet taken orally three times a day for 3 days.

2.2 Administration

XIFAXAN Tablets can be administered orally with or without food [see *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

XIFAXAN Tablets are pink-colored biconvex tablets and are available in the following strength:

- 200 mg – a round tablet debossed with "Sx" on one side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

XIFAXAN Tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN Tablets.

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5 WARNINGS AND PRECAUTIONS

5.1 Travelers' Diarrhea Not Caused by *Escherichia coli*

XIFAXAN Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

XIFAXAN Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

XIFAXAN Tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN Tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

5.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN Tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Development of Drug Resistant Bacteria

Prescribing XIFAXAN Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Travelers' Diarrhea

The safety of XIFAXAN Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving three or four days of treatment with XIFAXAN Tablets. The population studied had a mean age of 31.3 (18-79) years of which approximately 3% were ≥ 65 years old, 53% were male and 84% were White, 11% were Hispanic.

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Discontinuations of XIFAXAN Tablets 200 mg TID due to adverse reactions occurred in 0.4% of patients. The adverse reactions leading to discontinuation were taste loss, dysentery, weight decrease, anorexia, nausea and nasal passage irrigation.

All adverse reactions for XIFAXAN Tablets 200 mg TID that occurred at a frequency ≥ 2% in the two placebo-controlled trials combined are provided in Table 1. (These include adverse reactions that may be attributable to the underlying disease.)

Table 1. All Adverse Reactions With an Incidence ≥2% Among Patients Receiving XIFAXAN Tablets, 200 mg Three Times Daily, in Placebo-Controlled Studies

	Number (%) of Patients	
MedDRA Preferred Term	**XIFAXAN Tablets, 600 mg/day (N = 320)**	**Placebo N = 228**
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

The following adverse reactions, presented by body system, have also been reported in <2% of patients taking XIFAXAN Tablets in the two placebo-controlled clinical trials where the 200 mg was taken three times a day for travelers' diarrhea was used. The following includes adverse reactions regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: lymphocytosis, monocytosis, neutropenia

Ear and Labyrinth Disorders: ear pain, motion sickness, tinnitus

Gastrointestinal Disorders: abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort

General Disorders and Administration Site Conditions: chest pain, fatigue, malaise, pain NOS, weakness

Infections and Infestations: dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS

Injury and Poisoning: sunburn

Investigations: aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased

Metabolic and Nutritional Disorders: anorexia, dehydration

Musculoskeletal, Connective Tissue, and Bone Disorders: arthralgia, muscle spasms, myalgia, neck pain

Nervous System Disorders: abnormal dreams, dizziness, migraine NOS, syncope, loss of taste

Psychiatric Disorders: insomnia

Renal and Urinary Disorders: choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea

Skin and Subcutaneous Tissue Disorders: clamminess, rash NOS, sweating increased

Vascular Disorders: hot flashes NOS

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of XIFAXAN Tablets. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to XIFAXAN.

General: hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus. These events occurred as early as within 15 minutes of drug administration.

7 DRUG INTERACTIONS

Based on the results of these studies in healthy volunteers and *in vitro* induction and inhibition studies using human liver fractions, no clinically relevant drug interactions are anticipated with XIFAXAN Tablets [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well controlled studies in pregnant women. XIFAXAN Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose for travelers' diarrhea [600 mg/day], adjusted for body surface area) and in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose for travelers' diarrhea [600 mg/day], adjusted for body surface area). These effects include cleft palate, agnatha, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae.

8.3 Nursing Mothers

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of XIFAXAN Tablets in pediatric patients with Travelers' Diarrhea less than 12 years of age have not been established.

8.5 Geriatric Use

Clinical studies of XIFAXAN Tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects.

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8.6 Renal Insufficiency

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

8.7 Hepatic Insufficiency

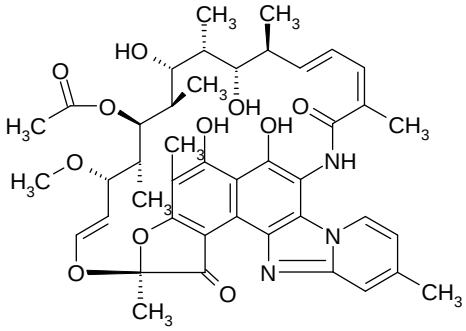
The pharmacokinetics of rifaximin were evaluated in patients with hepatic encephalopathy or mild to moderate hepatic impairment (Child Pugh A and B). An increase in systemic exposure to rifaximin in patients with hepatic impairment was seen in these studies, but no dosing adjustment with XIFAXAN Tablets is necessary due to its limited systemic absorption [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

No specific information is available on the treatment of overdosage with XIFAXAN Tablets. In clinical studies at doses higher than the recommended dose (> 600 mg/day for travelers' diarrhea), adverse reactions were similar in subjects who received doses higher than the recommended dose and placebo. In the case of overdosage, discontinue XIFAXAN Tablets, treat symptomatically, and institute supportive measures as required.

11 DESCRIPTION

XIFAXAN Tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-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]pyrido[1,2-á]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN Tablets for oral administration are film-coated and contain 200 mg of rifaximin.

Inactive ingredients: Each tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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Rifaximin is a rifamycin antibacterial drug [see *Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

The mean plasma pharmacokinetic parameters of rifaximin in 14 healthy subjects after a single oral 400 mg dose given as 2 x 200 mg doses and a single 550 mg dose in 12 healthy subjects under fed and fasting conditions are summarized in Table 2.

Table 2. Effect of Food on the Mean ± S.D. Pharmacokinetic Parameters

	Single 400 mg Dose of Rifaximin (N = 14)		**Single 550 mg Dose of Rifaximin (N= 12)**	
Parameter	Fasting	Fed	Fasting	Fed
C_{max} (ng/mL)	3.80 ± 1.32	9.63 ± 5.93	4.04 ± 1.51	4.76 ± 4.25
T_{max} (h)	1.21 ± 0.47	1.90 ± 1.52	0.75 (0.50-2.05)*	1.50 (0.50-4.08)*
Half-Life (h)	5.85 ± 4.34	5.95 ± 1.88	1.83 ± 1.38	4.84 ± 1.34
AUC (ng·h/mL)	18.35 ± 9.48	34.70 ± 9.23	11.1 ± 4.15	22.5 ± 12.0

*Median (range)

Because systemic absorption of rifaximin was minimal in both the fasting state and when administered within 30 minutes of a high-fat breakfast, XIFAXAN Tablets can be administered with or without food [see *Dosage and Administration (2.2)*].

Systemic absorption of rifaximin (XIFAXAN Tablets 200 mg three times daily) was also evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, $AUC_{0\text{-}last}$ estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. XIFAXAN Tablets are not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration [see *Warnings and Precautions (5.1)*].

Distribution

Animal pharmacokinetic studies have demonstrated that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for three days, concentrations of rifaximin in stools averaged ~8000 µg/g the day after treatment ended.

Metabolism

In vitro drug interactions studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce [see *Drug Interactions (7)]*.

In vitro study data suggest that rifaximin is a substrate for P-glycoprotein. Rifaximin is a weak inhibitor of P-gp; at concentrations (50 µM) significantly higher than those

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anticipated in plasma following oral dose administration, rifaximin only partially inhibited transport of a model P-gp substrate. Therefore, no clinically significant interactions with other drugs affected by P-glycoprotein are anticipated.

Excretion

400 mg ^{14}C-Rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 ± 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 ± 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were C_{max} 4.3 ± 2.8 ng/mL and AUC_t 19.5 ± 16.5 ng•h/mL with a median T_{max} of 1.25 hours.

Drug Interactions

Since rifaximin was shown to induce CYP3A4 *in vitro*, drug interaction studies in healthy volunteers were conducted with midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on these CYP3A4 substrates.

Two clinical drug-drug interaction studies were conducted with the rifaximin 200 mg tablet.

Midazolam

An open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and Q8H for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

Oral Contraceptives

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin [see *Drug Interactions (7)*].

Based on the results of the interaction studies in healthy volunteers and *in vitro* induction and inhibition studies using human liver fractions, no clinically relevant drug interactions are anticipated with XIFAXAN Tablets [see *Drug Interactions (7)]*.

12.4 Microbiology

Mechanism of Action

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Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the *Indications and Usage (1)* section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6 [see *References (15)*]. However, the correlation between susceptibility testing and clinical outcome has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 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 daily dose of 200 mg TID, 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, 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, adjusted for body surface area).

14 CLINICAL STUDIES

14. 1 Travelers' Diarrhea

The efficacy of XIFAXAN Tablets given as 200 mg orally taken three times a day for 3 days was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled studies in adult subjects with travelers' diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before

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treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of XIFAXAN Tablets was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (TLUS) which was defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 3 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat population (ITT) of Study 1. The duration of diarrhea was significantly shorter in patients treated with XIFAXAN Tablets than in the placebo group. More patients treated with XIFAXAN Tablets were classified as clinical cures than were those in the placebo group.

Table 3. Clinical Response in Study 1 (ITT population)

	XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5% CI)	P-Value
Median TLUS (hours)	32.5	58.6	1.78[a] (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7[b] (5.3, 32.1)	0.001

[a] Hazard Ratio
[b] Difference in rates

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stool after 72 hours of therapy) rates for Study 1 are presented in Table 4 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though XIFAXAN Tablets had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

Table 4. Microbiologic Eradication Rates in Study 1 Subjects with a Baseline Pathogen

	XIFAXAN	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
E. coli	38/53 (71.7)	40/54 (74.1)

Study 2 provided additional information to support the results presented for Study 1. This study also provided evidence that subjects treated with XIFAXAN Tablets with fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates than those without fever or blood in the stool at baseline. Many of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the subjects treated with XIFAXAN Tablets who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with

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Campylobacter jejuni isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated phase 1, open-label, pharmacokinetic study of oral XIFAXAN Tablets 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with XIFAXAN. Although this open-label challenge trial was not adequate to assess the effectiveness of XIFAXAN in the treatment of shigellosis, the following observations were noted.

Eight subjects received rescue treatment with ciprofloxacin either because of lack of response to XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1). Five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

15 REFERENCES

Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne PA. *Approved Standard NCCLS Document M7-A6* January 2003; 23 (2).

16 HOW SUPPLIED/STORAGE AND HANDLING

The 200 mg tablet is a pink-colored, round, biconvex tablet with “Sx” debossed on one side. It is available in the following presentations:

- NDC 65649-301-04, single blister unit (Professional Sample)
- NDC 65649-301-03, bottles of 30 tablets
- NDC 65649-301-41 bottles of 100 tablets
- NDC 65649-301-05 carton of 100 tablets, Unit Dose

Storage

Store XIFAXAN Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59-86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

17.1 Persistent Diarrhea

For those patients being treated for travelers’ diarrhea, XIFAXAN Tablets should be discontinued if diarrhea persists more than 24-48 hours or worsens, or if the patient has fever and/or blood in the stool the patient should seek medical care [see *Warnings and Precautions (5.1)*].

17.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN Tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon which may lead to *C. difficile*. Patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If diarrhea occurs after therapy or does not

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improve or worsens during therapy, patients should contact their physician as soon as possible [see *Warnings and Precautions (5.2)*].

17.3 Administration with Food

Patients should be informed that XIFAXAN Tablets may be taken with or without food.

17.4 Antibacterial Resistance

Patients should be counseled that antibacterial drugs including XIFAXAN Tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When XIFAXAN Tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by XIFAXAN Tablets or other antibacterial drugs in the future.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21361	SUPPL-11	SALIX PHARMACEUTICALS INC	XIFAXAN

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/s/

RENATA ALBRECHT
03/03/2010