XIFAXAN® (rifaximin) tablets, for oral use

Initial U.S. Approval: 2004

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

INDICATIONS AND USAGE

XIFAXAN is a rifamycin antibacterial indicated for:

- Treatment of travelers’ diarrhea (TD) caused by noninvasive strains of Escherichia coli in adult and pediatric patients 12 years of age and older (1.1, 5.1)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults (1.2)
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults (1.3)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.

Most common adverse reactions:

- TD (≥2%): Headache (6.1)
- HE (≥10%): Peripheral edema, nausea, diziness, fatigue, and ascites (6.1)
- IBS-D (≥2%): ALT increased, nausea (6.1)

Dosage and Administration

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

In the trials of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly.

DOSAGE FORMS AND STRENGTHS

200 mg and 550 mg tablets (3)

CONTRAINDICATIONS

History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of XIFAXAN (4)

WARNINGS AND PRECAUTIONS

- Travelers’ Diarrhea Not Caused by E. coli: XIFAXAN was not effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than E. coli. If diarrhea symptoms get worse or persist for more than 24 to 48 hours, discontinue XIFAXAN and consider alternative antibiotics (5.1)
- Clostridium difficile-Associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)
- Hepatic Impairment: Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.4, 8.7)
- Concomitant P-glycoprotein (P-gp) inhibitors (e.g., cyclosporine): Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor is needed (5.5, 7.1)

ADVERSE REACTIONS

Most common adverse reactions:

- TD (≥2%): Headache (6.1)
- HE (≥10%): Peripheral edema, nausea, diziness, fatigue, and ascites (6.1)
- IBS-D (≥2%): ALT increased, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 and www.Salix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Warfarin: Monitor INR and prothrombin time; dose adjustment of warfarin may be needed to maintain target INR range.

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.
2.4 Administration
XIFAXAN can be taken with or without food [see Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS
XIFAXAN is a pink-colored biconvex tablet and is available in the following strengths:

- 200 mg – a round tablet debossed with “Sx” on one side and plain on the other.
- 550 mg – an oval tablet debossed with “rfx” on one side and plain on the other.

4 CONTRAINDICATIONS
XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamicin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS
5.1 Travelers’ Diarrhea Not Caused by Escherichia coli
XIFAXAN was 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. Discontinue XIFAXAN if diarrhea symptoms get worse or persist more than 24 to 48 hours and alternative antibiotic therapy should be considered.

5.2 Clostridium difficile-Associated Diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, 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 for travelers’ diarrhea 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.

5.4 Severe (Child-Pugh Class C) Hepatic Impairment
There is increased systemic exposure in patients with severe hepatic impairment. The clinical trials were limited to patients with MELD scores <25. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh Class C) [see Use in Specific Populations (8.7), Clinical Studies (14.2)].

5.5 Concomitant Use with P-glycoprotein Inhibitors
Concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of XIFAXAN and a P-gp inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

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 200 mg taken three times a day was evaluated in patients with travelers’ diarrhea consisting of 320 patients in two placebo-controlled clinical trials with 95% of patients receiving three or four days of treatment with XIFAXAN. The population studied had a mean age of 31.3 (range: 18-79) years of which approximately 3% were ≥65 years old, 72% were female, 88% were White, 11% were Hispanic. The combined population studied had a mean age of 47 (range: 18 to 88) years of whom approximately 11% of the patients were ≥65 years old, 53% were male and 84% were White, 11% were Hispanic.

Discontinuations 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 irritation.

The adverse reaction that occurred at a frequency ≥2% in XIFAXAN-treated patients (n=320) at a higher rate than placebo (n=228) in the two placebo-controlled trials of TD was:
- headache (10% XIFAXAN, 9% placebo)

Hepatic Encephalopathy
The data described below reflect exposure to XIFAXAN 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 (range: 21 to 82) years; approximately 20% of the patients were ≥65 years old, 56% were male, 86% were White, and 4% were Black.

Ninety-one percent of patients in the trial were taking lactulose concomitantly. The most common adverse reactions that occurred at an incidence ≥5% and at a higher incidence in XIFAXAN-treated subjects than in the placebo group in the 6-month trial are provided in Table 1.

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>21 (15%) 13 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14%) 21 (13%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (13%) 13 (8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12%) 18 (11%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>16 (11%) 15 (9%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (9%) 11 (7%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (9%) 10 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (9%) 13 (8%)</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (7%) 8 (5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (8%) 6 (4%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (7%) 10 (6%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>9 (6%) 8 (5%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (6%) 4 (3%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (6%) 7 (4%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (6%) 5 (3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (5%) 6 (4%)</td>
</tr>
</tbody>
</table>

Table 1: Most Common Adverse Reactions* in HE Trial

*reported in ≥5% of Patients Receiving XIFAXAN and at a higher incidence than placebo

Irritable Bowel Syndrome with Diarrhea
The safety of XIFAXAN for the treatment of IBS-D was evaluated in 3 placebo-controlled studies in which 952 patients were randomized to XIFAXAN 550 mg three times a day for 14 days. Across the 3 studies, 96% of patients received at least 14 days of treatment with XIFAXAN. In Trials 1 and 2, 624 patients received only one 14-day treatment. Trial 3 evaluated the safety of XIFAXAN in 328 patients who received 1 open-label treatment and 2 double-blind repeat treatments of 14 days each over a period of up to 46 weeks. The combined population studied had a mean age of 47 (range: 18 to 88) years of whom approximately 11% of the patients were ≥65 years old, 72% were female, 88% were White, 9% were Black and 12% were Hispanic.

The adverse reaction that occurred at a frequency ≥2% in XIFAXAN-treated patients at a higher rate than placebo in Trials 1 and 2 for IBS-D was:
- nausea (3% XIFAXAN, 2% placebo)

The adverse reactions that occurred at a frequency ≥2% in XIFAXAN-treated patients (n=328) at a higher rate than placebo (n=308) in Trial 3 for IBS-D during the double-blind treatment phase were:
- ALT increased (XIFAXAN 2%, placebo 1%)
- anemia (XIFAXAN 2%, placebo 1%)

5.6 Common Adverse Reactions
The following adverse reactions, presented by body system, were reported in less than 2% of patients in clinical trials of TD and IBS-D and in less than 5% of patients in clinical trials of HE:

Hepatobiliary disorders: Clostridium colitis
Investigations: Increased blood creatine phosphokinase
Musculoskeletal and connective tissue disorders: myalgia

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of XIFAXAN. 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.

Infections and Infestations
Cases of C. difficile-associated colitis have been reported [see Warnings and Precautions (5.2)].

General
Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.
8.7 Hepatic Impairment
Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC) of rifaximin was about 10–14- and 21-fold higher in those patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), Clinical Studies (14.2)].

10 OVERDOSAGE
No specific information is available on the treatment of overdosage with XIFAXAN. In clinical studies at doses higher than the recommended dose (greater than 600 mg per day for TD, greater than 1100 mg per day for HE or greater than 1650 mg per day for IBS-D), adverse reactions were similar in subjects who received doses higher than the recommended dose and placebo. In the case of overdosage, discontinue XIFAXAN, treat symptomatically, and institute supportive measures as required.

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 (2S,16E,17S,21S,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-dione,25-acetate. The empirical formula is C43H51N3O11 and its molecular weight is 785.9. The chemical structure is represented below:

![Chemical Structure](https://example.com/structure.png)

XIFAXAN tablets for oral administration are film-coated and contain 200 mg or 550 mg of rifaximin.

Inactive ingredients:
- Each 200 mg tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmotearate, hypromellose, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.
- Each 550 mg tablet contains colloidal silicon dioxide, glycerol palmotearate, microcrystalline cellulose, polyethylene glycol/macrogel, polyvinyl alcohol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Rifaximin is an antibacterial drug [see Clinical Pharmacology (12.4)].

12.2 Pharmacokinetics
Absorption
In healthy subjects, the mean time to reach peak rifaximin plasma concentrations was about an hour and the mean tmax ranged 2.4 to 4 ng/mL after a single dose and multiple doses of XIFAXAN 550 mg.

Traveler’s Diarrhea
Systemic absorption of XIFAXAN (200 mg three times daily) was 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(tot) estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. XIFAXAN is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration [see Warnings and Precautions (5.1)].

Hepatic Encephalopathy
Mean rifaximin exposure (AUC(tot)) in patients with a history of HE was approximately 12-fold higher than that observed in healthy subjects. Among patients with a history of HE, the mean AUC in patients with Child-Pugh Class C hepatic impairment was 2-fold higher than in patients with Child-Pugh Class A hepatic impairment [see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)].

Irritable Bowel Syndrome with Diarrhea
In patients with irritable bowel syndrome with diarrhea (IBS-D) treated with XIFAXAN 550 mg three times a day for 14 days, the median Tmax was 1 hour and mean Cmax and AUC were generally comparable with those in healthy subjects. After multiple doses, AUC∞ was 1.65-fold higher than that on Day 1 in IBS-D patients (Table 2).
**Table 2. Mean (± SD) Pharmacokinetic Parameters of Rifaximin Following XIFAXAN 550 mg Three Times a Day in IBS-D Patients and Healthy Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>IBS-D Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-Dose (Day 1) n=12</td>
<td>Multiple-Dose (Day 14) n=14</td>
</tr>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>4.04 (1.51)</td>
<td>2.39 (1.28)</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>0.75 (0.5-2.1)</td>
<td>1.00 (0.5-2.0)</td>
</tr>
<tr>
<td>AUC\text{GI} (ng•h/mL)</td>
<td>10.4 (3.47)</td>
<td>9.30 (2.7)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>1.83 (1.38)</td>
<td>5.63 (5.27)</td>
</tr>
</tbody>
</table>

\[\text{* Median (range)}\]

**Table 3. Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class\(^1\)**

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects (n=14)</th>
<th>Child-Pugh Class A (n=18)</th>
<th>B (n=15)</th>
<th>C (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\text{GI} (ng•h/mL)</td>
<td>12.3 ± 4.8</td>
<td>118 ± 67.8</td>
<td>169 ± 55.7</td>
<td>257 ± 100.2</td>
</tr>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>3.4 ± 1.6</td>
<td>19.5 ± 11.4</td>
<td>25.4 ± 11.9</td>
<td>39.7 ± 13.4</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>0.8 (0.5, 4.0)</td>
<td>1 (0.9, 10)</td>
<td>1 (1.0, 4.2)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

\[\text{\(\text{a} \text{ Median (range)}\)}\]

**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 but did not significantly affect C\text{max}.

**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 was administered.

**Elimination**
The mean half-life of rifaximin in healthy subjects at steady-state was 5.6 hours and was 6 hours in IBS-D patients.

**Metabolism**
In an in vitro study rifaximin was metabolized mainly by CYP3A4. Rifaximin accounted for 18% of the radioactivity in plasma suggesting that the absorbed rifaximin undergoes extensive metabolism.

**Excretion**
In a mass balance study, after administration of 400 mg \(^{14}\)C-rifaximin orally to healthy volunteers, of the 96.94% total recovery, 96.62% of the administered radioactivity was recovered in feces mostly as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.

Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa.

**Specific Populations**

**Hepatic Impairment**
The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects.

The pharmacokinetics of rifaximin in patients with a history of HE was evaluated after administration of XIFAXAN 550 mg twice a day. The pharmacokinetic parameters were associated with a high variability and mean rifaximin exposure (AUC) of rifaximin by 2-fold but did not significantly affect C\text{max}.

**Cyclosporine**
In vitro in the presence of P-glycoprotein inhibitor, verapamil, the efflux ratio of rifaximin was reduced greater than 50%. In a clinical drug interaction study, mean C\text{max} for rifaximin was increased from 83-fold, from 0.48 to 40.0 ng/mL; mean AUC\text{GI} was increased 124-fold, from 2.54 to 314 ng•h/mL following co-administration of a single dose of XIFAXAN 550 mg with a single 600 mg dose of cyclosporine, an inhibitor of P-glycoprotein. See Drug Interactions (7.1).

Cyclosporine is also an inhibitor of OATP, breast cancer resistance protein (BCRP) and a weak inhibitor of CYP3A4. The relative contribution of inhibition of each transporter by cyclosporine to the increase in rifaximin exposure is unknown.

**Effect of rifaximin on other drugs**
In in vitro drug interaction studies the IC\text{50} values for rifaximin was >50 micromolar (~60 mcg) for CYP isosforms 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 2E1. In vitro IC\text{50} value of rifaximin for CYP3A4 was 25 micromolar. Based on in vivo studies, clinically significant drug interaction via inhibition of 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4 by rifaximin is not expected.

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

**Midazolam**
In an in vitro study, rifaximin was shown to induce CYP3A4 at the concentration of 0.2 micromolar. No significant induction of CYP3A4 enzyme using midazolam as a substrate was observed when rifaximin was administered three times a day for 7 days at 200 mg and 550 mg doses in two clinical drug interaction studies in healthy subjects. The effect of XIFAXAN 200 mg administered orally every 8 hours for 3 days and for 7 days on the pharmacokinetics of a single dose of either 2 mg intravenous midazolam or 6 mg oral midazolam was evaluated in healthy subjects. No significant difference was observed in the systemic exposure or elimination of intravenous or oral midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with XIFAXAN. Therefore, XIFAXAN was not shown to significantly affect intestinal or hepatic CYP3A4 activity for the 200 mg three times a day dosing regimen.

When single dose of 2 mg midazolam was orally administered after administration of XIFAXAN 550 mg three times a day for 7 days and 14 days to healthy subjects, the mean AUC of midazolam was 3.8% and 8.8% lower, respectively, than when midazolam was administered alone. The mean C\text{max} of midazolam was lower by 4 to 5% when XIFAXAN was administered for 7-14 days prior to midazolam administration. This degree of interaction is not considered clinically meaningful.

**Oral Contraceptives Containing Ethinyl Estradiol and Norgestimate**
The oral contraceptive study utilized an open-label, crossover design in 38 healthy female subjects to determine if XIFAXAN 200 mg orally administered three times a day for 3 days (the dosing regimen for travelers’ diarrhea) altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.5 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by XIFAXAN.

An open-label oral contraceptive study was conducted in 39 healthy female subjects to determine if XIFAXAN 550 mg orally administered three times a day for 7 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.025 mg of ethinyl estradiol (EE) and 0.25 mg norgestimate (NGM). Mean C\text{max} of EE and NGM was lower by 25% and 13%, after the 7-day XIFAXAN regimen than when the oral contraceptive was given alone. The mean AUC values of NGM active metabolites were reduced by 7% to approximately 11%, while AUC of EE was not altered in presence of rifaximin. The clinical relevance of the C\text{max} and AUC reductions in the presence of rifaximin is not known.

**12.4 Microbiology**

**Mechanism of Action**
Rifaximin is a semi-synthetic derivative of rifampin and acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase blocking one of the steps in transcription. This results in inhibition of bacterial protein synthesis and consequently inhibits the growth of bacteria.

**Drug Resistance and Cross-Resistance**
Resistance to rifaximin is caused primarily by mutations in the rop gene. This changes the binding site on DNA dependent RNA polymerase and decreases rifaximin binding affinity, thereby reducing efficacy. Cross-resistance between rifaximin and other classes of antimicrobials has not been observed.

**Antibacterial Activity**
Rifaximin has been shown to be active against the following pathogens both in vitro and in clinical studies of infectious diarrhea as described in the indications and Usage (1.1) section: Escherichia coli (enterotoxigenic and enteraggregative strains).

**Susceptibility Tests**
In vitro susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI). 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 per day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for TD, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for HE, 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 per day (doses equivalent to 1.2 to 16 times the recommended daily dose for TD and equivalent to 0.7 to 9 times the recommended daily dose for HE, 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 per day for TD, and approximately 2.6 times the clinical dose of 1100 mg per day for HE, adjusted for body surface area).

14 CLINICAL STUDIES

14.1 Travelers' Diarrhea

The efficacy of XIFAXAN 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 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 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 4 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat (ITT) population of Study 1. The duration of diarrhea was significantly shorter in patients treated with XIFAXAN than in the placebo group. More patients treated with XIFAXAN were classified as clinical cures than were those in the placebo group.

### Table 4. Clinical Response in Study 1 (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>XIFAXAN (n=125)</th>
<th>Placebo (n=129)</th>
<th>Estimate (97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TLUS (hours)</td>
<td>32.5</td>
<td>58.6</td>
<td>2.2 (1.28, 2.50)</td>
</tr>
<tr>
<td>Clinical cure, n (%)</td>
<td>99 (79)</td>
<td>78 (60)</td>
<td>19 (5.3, 32.1)</td>
</tr>
</tbody>
</table>

*a Hazard Ratio (p-value <0.001)

*b Difference in rates (p-value <0.01)

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

<table>
<thead>
<tr>
<th></th>
<th>XIFAXAN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>48/70 (69)</td>
<td>41/61 (67)</td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td>38/53 (72)</td>
<td>40/54 (74)</td>
</tr>
</tbody>
</table>

The results of Study 2 supported the results presented for Study 1. In addition, this study provided evidence that subjects treated with XIFAXAN 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 (diabetes-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 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 Campylobacter jejuni isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.*

In an unrelated open-label, pharmacokinetic study of oral XIFAXAN 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.

14.2 Hepatic Encephalopathy

The efficacy of XIFAXAN 550 mg taken orally twice a day was evaluated in a randomized, placebo-controlled, 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 298 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 asterisk 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 >19. Ninety percent of the patients were Child-Pugh Class C. Lactulose was concurrently 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 asterisk 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. Presented below in Figure 1 is the Kaplan-Meier event-free curve for all subjects (n=299) in the study.

Figure 1: Kaplan-Meier Event-Free Curves in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)

Note: Open diamonds and open triangles represent censored subjects.

1 Event-free refers to non-occurrence of breakthrough HE.

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 Class C (n=51), 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 (rifaximin) 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. Comparison of Kaplan-Meier estimates of event-free curves is shown in Figure 2.

Figure 2: Kaplan-Meier Event-Free Curves in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)
14.3 Irritable Bowel Syndrome with Diarrhea

The efficacy of XIFAXAN for the treatment of IBS-D was established in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients.

**Trial 1 and 2 - Design**

The first two trials, Trials 1 and 2, were of identical design. In these trials, a total of 1258 patients meeting Rome II criteria for IBS* were randomized to receive XIFAXAN 550 mg three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period. The Rome II criteria further categorizes IBS patients into 3 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or alternating IBS (bowel habits alternating between diarrhea and constipation). Patients with both IBS-D and alternating IBS were included in Trials 1 and 2. XIFAXAN is recommended for use in patients with IBS-D.

*Rome II Criteria: At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

1. Relieved with defecation; and/or 2. Onset associated with a change in frequency of stool; and/or 3. Onset associated with a change in form (appearance) of stool.

Symptoms that Cumulatively Support the Diagnosis of Irritable Bowel Syndrome:

- Abnormal stool frequency (for research purposes “abnormal” may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation);
- Passage of mucus;
- Bloating or feeling of abdominal distension.

**Trial 3 - Design**

Trial 3 evaluated repeat treatment in adults with IBS-D meeting Rome III criteria** for up to 46 weeks. A total of 2579 patients were enrolled to receive open-label XIFAXAN 550 mg three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period. The Rome III criteria further categorizes IBS patients into 3 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or alternating IBS (bowel habits alternating between diarrhea and constipation). Patients with both IBS-D and alternating IBS were included in Trials 1 and 2. XIFAXAN is recommended for use in patients with IBS-D.

**Rome III Criteria: Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) at least 3 days/month in last 3 months associated with two or more of the following: 1. Improvement with defecation; 2. Onset associated with a change in frequency of stool; 3. Onset associated with a change in form (appearance) of stool.
The response rate difference was 5.4% with 95% confidence interval (1.2% and 9.7%) with XIFAXAN and placebo treatment groups had similar baseline IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2 (see Table 7). A total of 636 patients subsequently had sign and symptom recurrence and were randomized to the double-blind phase. Of 1074 patients who experienced recurrence of their symptoms of abdominal pain or mushy/watery stool consistency for up to 20 treatment-free weeks. When patients experienced recurrence of their symptoms of abdominal pain or mushy/watery stool consistency for 3 weeks of a rolling 4-week period, they were randomized into the double-blind, placebo-controlled repeat treatment phase. Of 1074 patients who responded to open-label XIFAXAN, 382 experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time they discontinued, including patients who completed the 22 weeks after initial treatment with XIFAXAN. See Figure 3. Overall, 1257 of 2579 patients (49%) were nonresponders in the open-label phase and per the study protocol were withdrawn from the study. Other reasons for discontinuation include: patient request (5%), patient lost to follow-up (4%), adverse reaction (3%), and other (0.8%). There were 1074 (44%) of 2438 evaluable patients who responded to initial treatment with improvement in abdominal pain and stool consistency. The response rate for each IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2 (see Table 7). A total of 636 patients subsequently had sign and symptom recurrence and were randomized to the repeat treatment phase. The median time to recurrence for patients who experienced initial response during the open-label phase with XIFAXAN was 10 weeks (range 6 to 24 weeks).

The XIFAXAN (rifaximin) and placebo treatment groups had similar baseline IBS symptom scores at the time of recurrence and randomization to the double-blind phase, but symptom scores were less severe than at study entry into the open-label phase. Patients were deemed to have recurrent signs and symptoms by the following criteria: a return of abdominal pain or lack of stool consistency for at least 3 weeks during a 4-week follow-up period. The primary endpoint in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain and stool consistency as defined above during the 4 weeks following the first repeat treatment with XIFAXAN. The primary analysis was performed using the worst case analysis method where patients with <4 days of diary entries in a given week are considered as non-responders for that week. More patients receiving XIFAXAN were monthly responders for abdominal pain and stool consistency in the primary analysis in Trial 3 (see Table 8).

### Table 8. Efficacy Responder Rates in Trial 3 in a Given Week for at Least 2 Weeks During Weeks 3 to 6 of the Double-Blind, First Repeat Treatment Phase

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=308)</th>
<th>XIFAXAN (n=328)</th>
<th>Treatment Difference (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Responder&lt;sup&gt;b&lt;/sup&gt;, Abdominal Pain and Stool Consistency Responder&lt;sup&gt;c&lt;/sup&gt;</td>
<td>97 (31)</td>
<td>125 (38)</td>
<td>7% (0.9%, 16.9%)</td>
</tr>
<tr>
<td>Abdominal Pain Responders (≥30% reduction in abdominal pain)</td>
<td>130 (42)</td>
<td>166 (51)</td>
<td>9% (1.6%, 17.0%)</td>
</tr>
<tr>
<td>Stool Consistency Responders (≥50% reduction from baseline in days/week with loose or watery stools)</td>
<td>154 (50)</td>
<td>170 (52)</td>
<td>-2% (-4.7%, 11.0%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Confidence intervals were derived based on CMH test adjusting for center and patients' time to recurrence during maintenance phase.

<sup>b</sup> Primary endpoint

<sup>c</sup> Subjects were IBS-related abdominal pain and stool consistency responders if they were both weekly IBS-related abdominal pain responders and weekly stool consistency responders in a given week for at least 2 weeks during Weeks 3 to 6 in the double-blind first repeat treatment phase. Weekly responder in IBS-related abdominal pain was defined as a 30% or greater improvement from baseline in the weekly average abdominal pain score. Weekly responder in stool consistency was defined as a 50% or greater reduction in the number of days in a week with stool consistency of type 6 or 7 compared with baseline. The p-value for this composite endpoint was <0.05.

Thirty six of 308 (11.7%) of placebo patients and 56 of 328 (17.1%) of XIFAXAN-treated patients responded to the first repeat treatment and did not have recurrence of signs and symptoms through the treatment-free follow-up period (10 weeks after first repeat treatment). The response rate difference was 5.4% with 95% confidence interval (1.2% to 11.6%).