HE = hepatic encephalopathy.

INDICATION
XIFAXAN® (rifaximin) 550 mg tablets are indicated for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.

IMPORTANT SAFETY INFORMATION
• XIFAXAN is not for everyone. Do not take XIFAXAN if you have a known hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN.
• If you take antibiotics, like XIFAXAN, there is a chance you could experience diarrhea caused by an overgrowth of bacteria (C. difficile). This can cause symptoms ranging in severity from mild diarrhea to life-threatening colitis. Contact your healthcare provider if your diarrhea does not improve or worsens.
• Talk to your healthcare provider before taking XIFAXAN if you have severe hepatic (liver) impairment, as this may cause increased effects of the medicine.
• Tell your healthcare provider if you are taking drugs called P-glycoprotein and/or OATPs inhibitors (such as cyclosporine) because using these drugs with XIFAXAN may lead to an increase in the amount of XIFAXAN absorbed by your body.

Please see additional Important Safety Information on following page and accompanying full Prescribing Information.
99% of commercially insured patients have coverage

Plus, XIFAXAN is covered for 94% of Medicare patients, and those eligible for both Medicare and Medicaid may receive XIFAXAN for $8.35/month.¹

Visit www.healthcare.gov to see if you qualify for Medicaid.

Save on prescriptions now and later*

Most eligible, commercia...
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), 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)
- 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)

Limitations of Use
- TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli (1.1, 5.1)
- IBS-D: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli (1.1, 5.1)

- XIFAXAN can be taken with or without food. (2.4)

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD (2.1)</td>
<td>One 200 mg tablet 3 times a day for 3 days</td>
</tr>
<tr>
<td>HE (2.2)</td>
<td>One 550 mg tablet 2 times a day</td>
</tr>
<tr>
<td>IBS-D (2.3)</td>
<td>One 550 mg tablet 3 times a day for 14 days. Patients who experience recurrence can be retreated up to two times with the same regimen.</td>
</tr>
</tbody>
</table>

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

200 mg and 550 mg tablets (3)

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

- Contraindicated in patients with known 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 Encephalopathy: 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, dizziness, 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.

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

Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2018

-------------------------------------------------------------------------------------- FULL PRESCRIBING INFORMATION: CONTENTS* --------------------------------------------------------------------------------------

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
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12 CLINICAL PHARMACOLOGY
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*Sections or subsections omitted from the full prescribing information are not listed

DIFFERENCES IN THE TREATMENT EFFECT OF THOSE PATIENTS NOT USING LACTULOSE CONCOMITANTLY COULD NOT BE ASSESSED.

XIFAXAN has not been studied in patients with MELD (Model for End-Stage Liver Disease) scores >25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure in patients with more severe hepatic dysfunction [see Warnings and Precautions (5.4), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

1.3 Irritable Bowel Syndrome with Diarrhea

XIFAXAN is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

2 DOSAGE AND ADMINISTRATION
2.1 Dosage for Travelers’ Diarrhea

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

2.2 Dosage for Hepatic Encephalopathy

The recommended dose of XIFAXAN is one 550 mg tablet taken orally two times a day.

2.3 Dosage for Irritable Bowel Syndrome with Diarrhea

The recommended dose of XIFAXAN is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.
2.4 Administration
XIFAXAN can be taken with or without food [see Clinical Pharmacology (12.3)].

3 DOSE 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 “rX” on one side and plain on the other.

4 CONTRAINDICATIONS
XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angiokeratomas, 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.

The data described below reflect exposure to XIFAXAN in 348 patients, including 265
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 (18-79) years of which approximately 3%
were White, 9% were Black and 12% were Hispanic.

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 antibiotic treatment 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 rifampin can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of rifaximin 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 (18-79) years of which approximately 3% 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)
- nausea (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 twice 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, 61% 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>XIFAXAN Tablets</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>550 mg TWICE DAILY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=140</td>
<td>n=159</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21 (15%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14%)</td>
<td>21 (13%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (13%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12%)</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>16 (11%)</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (9%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (9%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (9%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (8%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (7%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>9 (6%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (6%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (6%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (6%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (5%)</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

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%)
- nausea (XIFAXAN 2%, placebo 1%)

Less 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, angioedema and urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.
7 DRUG INTERACTIONS

7.1 P-glycoprotein Inhibitors
Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs significantly increased the systemic exposure of rifaximin. 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. Caution should be exercised when concomitant use of XIFAXAN and a P-gp inhibitor such as cyclosporine is needed [see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)].

7.2 Warfarin
Changes in INR have been reported postmarketing in patients receiving rifaximin and warfarin concomitantly. Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.

7.3 CYP3A4 Substrates
An in vitro study has suggested that rifaximin induces CYP3A4 [see Clinical Pharmacology (12.3)]. However, in patients with normal liver function, XIFAXAN at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on XIFAXAN use in pregnant women to inform any drug associated risks. Teratogenic effects were observed in animal reproduction studies following administration of rifaximin to pregnant rats and rabbits during organogenesis at doses approximately 0.9 to 5 times and 0.7 to 33 times, respectively of the recommended human doses of 600 mg to 1650 mg per day. In rabbits, ocular, oral and maxillofacial, cardiac, and lumbar spine malformations were observed. Ocular malformations were observed in both rats and rabbits at doses that caused reduced maternal body weight gain [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data
Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the recommended dose for TD [600 mg per day], and approximately 1.3 to 2.6 times the recommended dose for HE [1100 mg per day], and approximately 0.9 to 1.8 times the recommended dose for IBS-D [1650 mg per day]) adjusted for body surface area. Rifaximin was teratogenic in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the recommended dose for TD [600 mg per day], and approximately 1.1 to 18 times the recommended dose for HE [1100 mg per day], and approximately 0.7 to 12 times the recommended dose for IBS-D [1650 mg per day]) adjusted for body surface area. These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebral.

A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses of rifaximin up to 300 mg/kg per day (approximately 5 times the recommended dose for TD [600 mg per day], and approximately 2.6 times the recommended dose for HE [1100 mg per day], and approximately 1.8 times the recommended dose for IBS-D [1650 mg per day]) adjusted for body surface area).

8.2 Lactation

Risk Summary
There is no information regarding the presence of rifaximin in human milk, the effects of rifaximin on the breastfed infant, or the effects of rifaximin on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for XIFAXAN and any potential adverse effects on the breastfed infant from XIFAXAN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of XIFAXAN has not been established in pediatric patients less than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D.

8.5 Geriatric Use

Of the total number of patients in the clinical study of XIFAXAN for HE, 19% of patients were 65 and over, while 2% were 75 and over. In the clinical studies of IBS-D, 11% of patients were 65 and over, while 2% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects for either indication. Clinical studies with XIFAXAN for TD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

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

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(0–t)) 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.

11 DESCRIPTION


![](image)

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 palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.
Each 550 mg tablet contains colloidal silicon dioxide, glycerol palmitostearate, microcrystalline cellulose, polyethylene glycol/macrogol, 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)].

12.3 Pharmacokinetics

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

Travelers’ 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(0–t) 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(t)) 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(t) was 1.65-fold higher than that on Day 1 in IBS-D patients (Table 2).
administration of Xifaxan 550 mg twice a day. The pharmacokinetic parameters were evaluated after a history of HE was evaluated after a history of HE was evaluated after hepatic impairment compared to healthy subjects.

### Hepatic Impairment

Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was recovered in feces mostly as the unchanged drug and 0.32% was recovered in urine for 18% of radioactivity in plasma suggesting that the absorbed rifaximin undergoes extensive metabolism.

### Excretion

In a mass balance study, after administration of 400 mg 14C-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 in healthy subjects 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) in patients with a history of HE was higher compared to those in healthy subjects. The mean AUC in patients with hepatic impairment of Child-Pugh Class A, B, and C was 10-, 14-, and 21-fold higher, respectively, compared to that in healthy subjects (Table 3).

### Oral Contraceptives Containing Ethinyl Estradiol and Norgestimate

In an oral contraceptive study utilizing an open-label, crossover design in 28 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 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_{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 lower by 7% to approximately 11%, while AUC of EE was not altered in presence of rifaximin. The clinical relevance of the C_{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 rpoB 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.

### 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 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 those in the placebo group.

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

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Clinical cure, n (%)</td>
<td>99 (79)</td>
<td>78 (60)</td>
</tr>
</tbody>
</table>

\(^{2}\) Hazard Ratio (p-value <0.001)

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>Pathogen</th>
<th>XIFAXAN</th>
<th>Placebo</th>
<th>Estimate (97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>38/55 (72)</td>
<td>40/54 (74)</td>
<td></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 (dysesthesia-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, from 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, multi-site 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 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 ≥19.

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. 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](image)

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.
13.4 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-D were randomized to receive XIFAXAN 550 mg or placebo three times a day (n=634) or placebo (n=624) 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 or more of the following: 1. Relief 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.

**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.

Symptoms that Cumulatively Support the Diagnosis of Irritable Bowel Syndrome:

- Abnormal stool frequency (for research purposes “abnormal” may be defined as two or more abnormal stools per day and less than 3 bowel movements per day); 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 were enrolled to receive open-label XIFAXAN for 14 days. Of 2438 evaluable patients, 1074 (44%) responded to initial treatment and were evaluated over 22 weeks for continued response or recurrence of IBS-symptoms. A total of 636 patients had symptom recurrence and were randomized into the double-blind phase of the study. These patients were scheduled to receive XIFAXAN 550 mg three times a day (n=328) or placebo (n=308) for two additional 14-day repeat treatment courses separated by 10 weeks. See Figure 3.

Figure 3: Trial 3 Study Design

The IBS-D population from the three studies had mean age of 47 (range: 18 to 88) years of which approximately 11% of patients were ≥65 years old, 72% were female and 88% were White.

Trials 1 and 2 - Results

Trials 1 and 2 included 1258 IBS-D patients (309 XIFAXAN, 314 placebo); (315 XIFAXAN, 320 placebo). The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. Adequate relief was defined as a response of “yes” to the following weekly Subject Global Assessment (SGA) question: “In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? (Yes/No).

Adequate relief of IBS symptoms was experienced by more patients receiving XIFAXAN than those receiving placebo during the month following 2 weeks of treatment (SGA-IBS Weekly Results: 41% vs. 31%, p=0.0125; 41% vs. 32%, p=0.0263 (See Table 6).

Table 6. Adequate Relief of IBS Symptoms During the Month Following Two Weeks of Treatment

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIFAXAN</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n=309</td>
<td>n=314</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adequate Relief of IBS Symptoms</td>
<td>126 (41)</td>
<td>98 (31)</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)*</td>
<td>10%</td>
<td>(2.1%, 17.1%)</td>
</tr>
</tbody>
</table>

Table 7. Efficacy Responder Rates in Trial 1 and 2 During the Month Following Two Weeks of Treatment

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIFAXAN</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n=315</td>
<td>n=320</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>144 (47)</td>
<td>121 (39)</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>8%</td>
<td>(0.3%, 15.9%)</td>
</tr>
<tr>
<td>Abdominal Pain Responders</td>
<td>159 (51)</td>
<td>132 (42)</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>9%</td>
<td>(1.8%, 17.5%)</td>
</tr>
<tr>
<td>Stool Consistency Responders</td>
<td>244 (79)</td>
<td>212 (68)</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>11%</td>
<td>(4.4%, 18.2%)</td>
</tr>
</tbody>
</table>

* Confidence Interval

b The p-value for the primary endpoint for Trial 1 and for Trial 2 was <0.05.

The trials examined a composite endpoint which defined responders by IBS-related abdominal pain and stool consistency measures. Patients were monthly responders if they met both of the following criteria:

- experienced a ≥30% decrease from baseline in abdominal pain for ≥2 weeks during the month following 2 weeks of treatment
- had a weekly mean stool consistency score ≤4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment

More patients receiving XIFAXAN were monthly responders for abdominal pain and stool consistency in Trials 1 and 2 (see Table 7).
In TARGET 3, 2579 patients were scheduled to receive an initial 14-day course of open-label XIFAXAN followed by 4 weeks of treatment-free follow-up. At the end of the follow-up period, patients were assessed for response to treatment. Patients were considered a responder if they achieved both of the following:

- at least a 30% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale type 6 or 7 compared with baseline where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces; entirely liquid.
- Stool consistency responders in a given week for at least 2 weeks during Weeks 3 to 6

The XIFAXAN (rifaximin) and placebo treatment groups had similar baseline IBS-related abdominal pain and stool consistency as defined above during the 4 weeks following the first repeat treatment with XIFAXAN. The primary analysis in Trial 3 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-week follow-up period. The primary endpoint in the double-blind, placebo-controlled repeat treatment phase of TARGET 3 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

|                   | Placebo (n=308) (%) | XIFAXAN (n=328) (%) | Treatment Difference (95% CI)
|-------------------|---------------------|---------------------|---------------------
| Abdominal Pain Responders<sup>a</sup> | 97 (31)              | 125 (38)            | 7% (0.9%, 16.9%)     |
| Stool Consistency Responders<sup>b</sup> | 130 (42)            | 166 (51)            | 9% (1.6%, 17.0%)     |
| Abdominal Pain Responders<sup>c</sup> (≥30% reduction in abdominal pain) | 154 (50)            | 170 (52)            | 2% (-4.7%, 11.0%)   |

<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 50% 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%).