**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, 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.

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**RECENT MAJOR CHANGES**

Indications and Usage, Irritable Bowel Syndrome with Diarrhea (1.3) 5/2015

Dosage and Administration, Irritable Bowel Syndrome with Diarrhea (2.3) 5/2015

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**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.
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

**WARNINGS AND PRECAUTIONS**

Most common adverse reactions:
- TD (2%): Headache
- HE (10%): Peripheral edema, nausea, dizziness, fatigue, and ascites
- IBS-D (2%): ALT increased, nausea

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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**Dosage and Administration**

- **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)
- **HE**: Caution should be exercised when concomitant use of rifaximin is anticipated. Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.1, 5.2, 5.4). Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5, 7.2)
- **IBS-D**: Do not use in patients with irritable bowel syndrome with diarrhea due to pathogens other than *Escherichia coli* (1.1, 5.1)

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**Dosage Forms and Strengths**

- **200 mg**: A round tablet debossed with “Sx” on one side.
- **550 mg**: A pink-colored biconvex tablet and is available in the following strengths:
  - 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.

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**Contraindications**

- **200 mg and 550 mg tablets (3)**

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**Directions**

- **HE**: Caution should be exercised when concomitant use of rifaximin is anticipated. Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.1, 5.2, 5.4). Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5, 7.2)

---

**Dosage and Administration**

- **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)
- **HE**: Caution should be exercised when concomitant use of rifaximin is anticipated. Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.1, 5.2, 5.4). Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5, 7.2)

---

**ADVERSE REACTIONS**

Most common adverse reactions:
- TD (2%): Headache
- HE (10%): Peripheral edema, nausea, dizziness, fatigue, and ascites
- IBS-D (2%): ALT increased, nausea

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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**Indications and Usage**

XIFAXAN is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults (1.2)

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**Precautions (5.1)**

- **HE**: Caution should be exercised when concomitant use of rifaximin is anticipated. Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.1, 5.2, 5.4). Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5, 7.2)

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**Clinical Pharmacology (12.3)**

Most common adverse reactions:
- TD (2%): Headache
- HE (10%): Peripheral edema, nausea, dizziness, fatigue, and ascites
- IBS-D (2%): ALT increased, nausea

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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**Use in Specific Populations**

Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2015
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. Hypertoxic production strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibiotic 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 inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitantly using XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-glycoprotein inhibitors may further increase the systemic exposure to rifaximin [see Drug Interactions (7.2), Pharmacokinetics (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 520 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: 6-94) years of whom approximately 65% were male and 86% were White, 11% were Hispanic. The population studied had a mean age of 56 (range: 18 to 88) years of whom approximately 53% were male and 84% were White, 11% were Hispanic. There were no significant differences between placebo and XIFAXAN in the percentage of patients with the various adverse reactions. No occurrences of Clostridium difficile-associated colitis were observed.

Irritable Bowel Syndrome with Diarrhea

The safety of XIFAXAN for the treatment of IBS-D was evaluated in three placebo-controlled studies in which 292 patients were randomized to XIFAXAN 550 mg three times a day for 7 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 either XIFAXAN or placebo. The evaluation of 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, 36% 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 reaction that occurred at a frequency ≥2% in XIFAXAN-treated patients (n=322) 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%)


7 DRUG INTERACTIONS

7.1 Effects of XIFAXAN on Other Drugs

Rifaximin is not expected to inhibit cytochrome P450 isoforms 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 in clinical use based on in vitro studies [see Clinical Pharmacology (12.3)].

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.

7.2 Effects of Other Drugs on XIFAXAN

In vitro studies suggested that rifaximin is a substrate of P-glycoprotein, OATP1A2, OATP1B1 and OATP1B3. Concomitant cyclosporine as an inhibitor of P-glycoprotein and OATPs, significantly increased the systemic exposure to rifaximin.

Cyclosporine Co-administration of cyclosporine, with XIFAXAN resulted in 83-fold and 124-fold increases in rifaximin mean C\text{max} and AUC\text{t last}, in healthy subjects. The clinical significance of this increase in systemic exposure is unknown [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)].

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 and 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, oral, oral and rectal administration of rifaximin, and lumbar spinal malformations were observed. Occur malformations have been 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 mg/kg to 300 mg/kg (approximately 5 to 50 times the recommended dose for TD [600 mg per day], and approximately 1.3 to 2.6 times the recommended dose for HD [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 15 times the recommended dose for HD [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 vertebrae.

A pre and postrnatal development study in rats showed no evidence of any adverse effect on pre- and postrnatal development or 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 HD [1100 mg per day], and approximately 1.6 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 BD.

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.

Table 1: Most Common Adverse Reactions* in HE Trial

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>21 (15%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (13%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>
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 to 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) 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 (12.5), Clinical Studies (14.2)].

10 OVERDOSAGE

No specific information is available on the treatment of overdose 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 overdose, discontinue XIFAXAN, 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 (2R,4R,7R,10S) - (−)-6-aminomethyl-2,7-(epoxypentadeca-1,11,13-trienimino)benzofuro[4,5-e][1,4]benzoxazepine. The molecular formula is C31H31N5O11 and its molecular weight is 514.53.

Rifaximin is a white to off-white, crystalline powder. XIFAXAN tablets are scored and film-coated with the following inactive ingredients: crosslinked sodium carboxymethyl cellulose, hypromellose, 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 values were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.34 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) 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 (5.7)].

Irritable Bowel Syndrome with Diarrhea

Rifaximin concentrations after 3 and 9 consecutive doses ranged following repeated administration for 3 days (9 doses). Peak plasma suggesting that the absorbed rifaximin undergoes metabolism. The chemical structure is represented below.

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.

Food Effect in Healthy Subjects

In a high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects, 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 Cmax.

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 radioactivity in the unchanged drug.

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 0.05% 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) 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 were 10-, 14-, and 21-fold higher, respectively, compared to that in healthy subjects (Table 3).

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

<table>
<thead>
<tr>
<th>Child-Pugh Class</th>
<th>Healthy Subjects</th>
<th>AUC (ng•h/mL)</th>
<th>Cmax (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=18)</td>
<td>12.3 ± 4.8</td>
<td>118 ± 67.8</td>
<td>109 ± 55.7</td>
</tr>
<tr>
<td>B (n=15)</td>
<td>3.4 ± 1.6</td>
<td>19.5 ± 11.4</td>
<td>25.4 ± 11.9</td>
</tr>
<tr>
<td>C (n=4)</td>
<td>3.0 ± 0.5</td>
<td>6.0 ± 3.7</td>
<td>9.7 ± 3.4</td>
</tr>
</tbody>
</table>

1 Cross-study comparison with pharmacokinetic parameters in healthy subjects.

1 Median (range)

Renal Impairment

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

Drug Interaction Studies

Effect of other drugs on rifaximin

An in vitro study suggests that rifaximin is a substrate of CYP3A4.

In vitro rifaximin is a substrate of P-glycoprotein, OATP1A2, OATP1B1, and OATP1B3. Rifaximin is not a substrate of OATP2B1.

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 Cmax for rifaximin was increased 83-fold, from 0.45 to 40.0 ng/mL, mean AUC was increased 12-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 (7.2)].

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 to cyclosporine to the increase in rifaximin exposure is unknown.

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>Subjects</th>
<th>Healthy Subjects</th>
<th>IBS-D Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after dose</td>
<td>Single-Dose Day 1</td>
<td>Single-Dose Day 14</td>
</tr>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2.39 ± 0.85</td>
<td>1.36 ± 0.97</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.00 (0.5-2.0)</td>
<td>1.00 (0.5-2.0)</td>
</tr>
<tr>
<td>AUC</td>
<td>14.0 ± 2.47</td>
<td>9.30 ± 2.77</td>
</tr>
<tr>
<td>AUC (ng•h/mL)</td>
<td>7.93 ± 1.36</td>
<td>5.63 ± 2.67</td>
</tr>
</tbody>
</table>

median (range)
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 28 healthy female subjects to determine if XIFAXAN 550 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 0.025 mg of ethinyl estradiol and 0.25 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 Cmax of EE and NGM was lower by 25% and 13%, after the 7-day XIFAXAN regimen than when the oral contraceptive was administered in the previous 6 months. 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 Cmax 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 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 *rpoG* 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 Cr: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 1500 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 hepatectomy 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 3000 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 (TLS) which was defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 4 displays the median TLS 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 compared to placebo. More patients treated with XIFAXAN were classified as clinical cures than were those in the placebo group.

<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 TLS (hours)</td>
<td>32.5</td>
<td>58.6</td>
<td>2* (1.26, 2.58)</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>

* Hazard Ratio (p-value <0.001)

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 TLS. 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 at baseline in the 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, not being different from placebo, rifaximin eradicated the isolates 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 manifest evidence of severe dysentery or relapse.

14.2 Hepatic Encephalopathy

The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a double-blind, placebo-controlled study in adult subjects with HE. The efficacy of XIFAXAN 550 mg in reducing the risk of breakthrough overt HE 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 of 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 have prolonged TLS. The following subpopulations due to small sample size: non-White (n=42), baseline MELD >19 (n=26), Child-Pugh Class C (n=31), and those without concomitant lactulose use (n=26).

HE-related hospitalizations (hospitalizations directly resulting from HE, or hospitalizations complicated by HE, or hospitalizations for 19 of 140 subjects (14%) and 36 of 159 subjects (23%) in the XIFAXAN and placebo groups respectively. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE-related hospitalizations by 50% during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves is shown in Figure 2.

#### Figure 2: Kaplan-Meier Event-Free Curves in Pivotal HE Study (Time to First HE-Related Hospitalization in HE Study 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 HE-related hospitalization.

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.

Trails 1 and 2 - Design

Two trials (Trials 1 and 2) were identical in design. In these trials, a total of 1258 patients meeting Rome II criteria for IBS* were randomized to receive XIFAXAN 550 mg
The IBS-D population from the three studies had an mean age of 47 (range: 18 to 88) years of which approximately 11% of patients were ≥65 years old, 72% were female and 48% were White.

**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.

Trials 1 and 2 - Results

Trials 1 and 2 enrolled 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 last 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=0.0052). 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>XIFAXAN (n=309)</th>
<th>Placebo (n=320)</th>
<th>Treatment Difference (96% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Relief of IBS Symptoms</td>
<td>126 (41)</td>
<td>98 (31)</td>
<td>28 (10%) (1.7%, 17.1%)</td>
</tr>
</tbody>
</table>

Trial 3 - Results

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 scheduled 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

Adequate relief of IBS symptoms during the month following two weeks of treatment was experienced by 144 (47) XIFAXAN vs. 121 (39) Placebo (8% (0.5%, 15.9%)).

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>XIFAXAN (n=309)</th>
<th>Placebo (n=314)</th>
<th>Treatment Difference (96% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>144 (47)</td>
<td>121 (39)</td>
<td>23 (7%) (0.3%, 14.9%)</td>
</tr>
<tr>
<td>Abdominal Pain Responders</td>
<td>159 (51)</td>
<td>132 (42)</td>
<td>27 (11%) (4.4%, 18.3%)</td>
</tr>
<tr>
<td>Stool Consistency Responders</td>
<td>244 (79)</td>
<td>212 (68)</td>
<td>32 (14%) (6.6%, 19.9%)</td>
</tr>
</tbody>
</table>

The XIFAXAN 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 repeat treatment phase was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain and stool consistency defined as above 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 Between Weeks 3 to 6 of the Double-Blind, First Repeat Treatment Phase

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=308)</th>
<th>XIFAXAN (n=328)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Responders*</td>
<td>97 (31)</td>
<td>125 (38)</td>
<td>28 (7%) (0.9%, 16.0%)</td>
</tr>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>130 (42)</td>
<td>166 (51)</td>
<td>36 (9%) (1.6%, 17.0%)</td>
</tr>
</tbody>
</table>

Note: *The 95% confidence intervals were based on CMH test adjusting for center and patients’ time to recurrence during maintenance phase.

Primary endpoint

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 508 (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%).
REFERENCES

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 65649-301-03, bottles of 30 tablets

The 550 mg tablet is a pink-colored, oval, biconvex tablet with “rfx” debossed on one side. It is available in the following presentations:
- NDC 65649-303-02, bottles of 60 tablets
- NDC 65649-303-03, carton of 60 tablets, Unit Dose
- NDC 65649-303-04, carton of 42 tablets, Unit Dose

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

PATIENT COUNSELING INFORMATION
Persistent Diarrhea
For those patients being treated for travelers’ diarrhea, discontinue XIFAXAN if diarrhea persists more than 24-48 hours or worsens. Advise the patient to seek medical care for fever and/or blood in the stool [see Warnings and Precautions (5.1)].

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 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 improve or worsens during therapy, advise patients to contact a physician as soon as possible [see Warnings and Precautions (5.4)].

Administration with Food
Inform patients that XIFAXAN may be taken with or without food.

Antibacterial Resistance
Counsel patients that antibacterial drugs including XIFAXAN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When XIFAXAN is 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 or other antibacterial drugs in the future.

Severe Hepatic Impairment
Inform patients with severe hepatic impairment (Child-Pugh Class C) that there is an increase in systemic exposure to XIFAXAN [see Warnings and Precautions (5.4)].

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Rifaximin for Travelers’ Diarrhea, Hepatic encephalopathy and IBS are protected by US Patent Nos. 7,045,620; 7,612,199; 7,902,206; 7,906,542; 8,158,781; 8,158,644; 8,193,196; 8,518,949; 8,741,904; 8,835,452; and 8,853,231. Rifaximin for Travelers’ Diarrhea is also protected by US Patent No. 7,928,115. Rifaximin for Hepatic encephalopathy is also protected by US Patent No. 8,462,573; 8,829,017; 8,946,252; and 8,969,398. Rifaximin for IBS is also protected by US Patent Nos. 6,861,053; 7,452,857; 7,718,608; and 8,309,569.

Web site: www.Salix.com