INDICATION

XIFAXAN® (rifaximin) 550 mg tablets are indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) 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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
WHAT IS IBS-D?

IBS-D stands for irritable bowel syndrome with diarrhea. Symptoms can vary over time and often include:

- **Abdominal Pain**
  Frequent stomach discomfort resulting in distraction from what matters

- **Diarrhea**
  Loose, mushy, or watery stools and/or frequent bowel movements

You are not alone

IBS-D is a common disorder of the large intestine (colon) that affects up to 16 million Americans

WHAT CAUSES IBS-D?

The exact cause of IBS-D is unknown, though various factors can play a role in creating symptoms. Your gut normally contains many types of bacteria that help digest the food you eat and keep you healthy.

A range of evidence suggests an imbalance in these bacteria may lead to symptoms of IBS-D.

Are there other causes?

There are many factors that may cause IBS-D symptoms, such as:

- Food sensitivity
- Inflammation in the intestines
- Abnormal intestinal contractions or spasms
- Improper signals between the brain and the intestines

IMPORTANT SAFETY INFORMATION (continued)

- 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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION (continued)

- Talk to your healthcare provider before taking XIFAXAN if you have severe hepatic (liver) impairment, as this may cause increased effects of the medicine.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
How does Xifaxan treat IBS-D?

Finding a treatment that addresses the symptoms as well as a possible cause may achieve lasting relief.

Xifaxan is the only FDA-approved treatment for IBS-D that alters bacteria in the gut.

Xifaxan works mainly in the gut to inhibit the growth of bacteria linked to IBS-D symptoms.

Only your healthcare provider can tell if your symptoms are caused by IBS-D and if Xifaxan may be right for you.

IMPORTANT SAFETY INFORMATION (continued)

• 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 throughout and accompanying full Prescribing Information.

What to expect while taking Xifaxan

Xifaxan is a 2-week treatment that provided up to 6 months of relief from abdominal pain and diarrhea, associated with IBS-D.†‡

Returning symptoms, when reported, were less severe after treatment with Xifaxan. If your symptoms come back, talk to your doctor about retreatment.

IMPORTANT SAFETY INFORMATION (continued)

• In clinical studies, the most common side effects of Xifaxan in IBS-D were nausea (feeling sick to your stomach) and an increase in liver enzymes.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
MOST COMMON SIDE EFFECTS

Patients taking XIFAXAN had similar side effects to those taking placebo.

In clinical studies, the most common side effects with XIFAXAN for IBS-D were:

• Nausea (feeling sick to your stomach)†
• An increase in liver enzymes‡

Constipation was observed in only 0.5% of XIFAXAN patients.

†Nausea was observed in 3% of patients.
‡Liver enzymes increase observed in 2% of patients.

XIFAXAN has a well-established Safety Profile

• 14 years of therapeutic use; studied in clinical trials across >3300 patients
• NOT a controlled substance
• NOT contraindicated in patients without a gallbladder
• No association of pancreatitis was observed in patients taking XIFAXAN in the clinical trials

Patients are finding relief that lasts, watch their stories at Xifaxan.com

HOW TO TAKE XIFAXAN

XIFAXAN is a short-term treatment that you take 3 times a day for 2 weeks

2 week treatment
UP TO 6 months of relief†

†In a clinical trial: range of 6 to 24 weeks; average of 10 weeks. You can be retreated up to 2 times if symptoms return.

Convenient dosing with lasting symptom relief†

• Take one XIFAXAN 550 mg tablet 3 times a day for 2 weeks§
• You can take with or without food
• Be sure to complete the entire 2-week course of treatment, even if you begin to feel better before you have finished
• You can be retreated up to 2 times if symptoms come back

§Always take XIFAXAN as directed by your healthcare provider.

IMPORTANT SAFETY INFORMATION (continued)

• XIFAXAN may affect warfarin activity when taken together. Tell your healthcare provider if you are taking warfarin because the dose of warfarin may need to be adjusted to maintain proper blood-thinning effect.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION (continued)

• If you are pregnant, planning to become pregnant, or nursing, talk to your healthcare provider before taking XIFAXAN because XIFAXAN may cause harm to an unborn baby or nursing infant.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
XIFAXAN has the best insurance coverage of any medication approved for IBS-D.

Most eligible, commercially insured patients may pay as little as $0. Applies to initial fills and refills. Activation is required.

98% of commercially insured patients and 94% of Medicare patients have coverage for XIFAXAN.

Patient is not eligible if he/she participates in or seeks reimbursement or submits a claim for reimbursement to any federal or state healthcare program with prescription drug coverage, such as Medicaid, Medicare, Medigap, VA, DOD, TRICARE, or any similar federal or state health care program (each a Government Program), or where prohibited by law. Patient must be enrolled in, and must seek reimbursement from or submit a claim for reimbursement to, a commercial insurance plan. Offer excludes full cash-paying patients. This offer may not be redeemed for cash. By using this offer, you are certifying that you meet the eligibility criteria and will comply with the terms and conditions described herein and will not seek reimbursement for any benefit received through this card. This offer is only good in the USA at participating retail pharmacies. This offer cannot be redeemed at other locations, including government-subsidized clinics or facilities. This offer is not valid where otherwise prohibited, taxes, or otherwise restricted. Patient is responsible for reporting receipt of co-pay assistance to any insurer, healthcare plan, or other third party who pays for or reimburses any part of the prescription filled using the co-pay card, as may be required. This offer cannot be combined with other offers. This offer is nontransferable. No substitutions are permitted. Salix Pharmaceuticals reserves the right to rescind, revoke, or amend this offer at any time without notice. This offer expires on December 31, 2019. Visit xifaxan.com or call 1-855-250-3759 for full eligibility criteria, terms and conditions.

IMPORTANT SAFETY INFORMATION (continued)

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch/ or call 1-800-FDA-1088.

For product information, adverse event reports, and product complaint reports, please contact:
Salix Product Information Call Center
Phone: 1-800-321-4576  |  Fax: 1-510-595-8183
Email: salixmc@dlss.com

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Salix Pharmaceuticals
400 Somerset Corporate Blvd., Bridgewater, NJ 08807

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**INDICATIONS AND USAGE**

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.

**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**

History of hypersensitivity to rifaximin, rifamycin antibiotic 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%): Vomiting, diarrhea, edema, nausea, dizziness, and ascites (6.1)
- IBS-D (≥6%): ALT increased, nausea (6.1)

**USE IN SPECIFIC POPULATIONS**

Pregnancy: May cause fetal harm (8.1)

**FULL PRESCRIBING INFORMATION: CONTENTS**

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
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See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2018

**FULL PRESCRIBING INFORMATION**

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

**1.1 Travelers’ Diarrhea**

XIFAXAN is indicated for the 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).

**Limitations of Use**

XIFAXAN should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than Escherichia coli (see Warnings and Precautions (5.1), Clinical Pharmacology (12.4), Clinical Studies (14.1)).

**1.2 Hepatic Encephalopathy**

XIFAXAN is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults. In the trials of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly.

**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.

**2.1 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 twice a day for 3 days.

**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 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 rifamycin 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.

XIFAXAN is not effective in cases of travelers’ diarrhea due to Campylobacter jejuni. The effectiveness of XIFAXAN in travelers’ diarrhea caused by Shigella spp. and Salmonella spp. has not been proven. XIFAXAN should not be used in patients where Campylobacter jejuni, Shigella spp., or Salmonella spp. may be suspected as causative pathogens [see Indications and Usage (1.1)].

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 99% 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% of patients were ≥65 years old, 53% were male and 84% were White, 11% were Hispanic. The combined population studied had a mean age of 47 (range: 18 to 88) years of which approximately 11% of the patients were ≥65 years old, 72% were female, 88% were White, 9% were Black and 12% were Hispanic.

The following adverse reactions have been identified during post-approval use of XIFAXAN. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to XIFAXAN.

<table>
<thead>
<tr>
<th>Adverse Reaction</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>Abdominal pain</td>
<td>12 (9%) 13 (8%)</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 upper</td>
<td>9 (6%) 8 (5%)</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (7%) 8 (5%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (7%) 10 (6%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (8%) 6 (4%)</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>Dyspea</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>

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.

8.3 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.

8.4 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.

8.5 Renal Impairment

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

8.6 Hepatic Impairment

Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC$_{\text{tau}}$) 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)].

10 OVERDOSE

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.

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,5R,13E,16S,18S)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-dienoate. The empirical formula is C$_{43}$H$_{51}$N$_3$O$_{11}$ and its molecular weight is 785.9. The chemical structure is represented below:
administration of Xifaxan 550 mg twice a day. The pharmacokinetic parameters were detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa. Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was mostly as metabolites with 0.03% as the unchanged drug.

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 volatilized as exhaled CO₂ and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.

Rifaximin is metabolized mainly by CYP3A4. Rifaximin accounted for 18% of the urinary excretion after administration of 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'-hydroxyxidamoxin, 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, when midazolam was administered alone. The mean Cmax 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.

Effect of rifaximin on other drugs

In an in vitro drug interaction 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'-hydroxyxidamoxin, 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.

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 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 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 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 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 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.

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 enteroaggregative 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 weight comparisons). There was no increase in tumors in Tg.rasH 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 the 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 (1.26, 2.50)</td>
</tr>
<tr>
<td>Clinical cure, n (%)</td>
<td>99 (79)</td>
<td>78 (60)</td>
<td>1.99 (5.3, 32.1)</td>
</tr>
</tbody>
</table>

a 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>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48/70 (69)</td>
<td>41/61 (67)</td>
</tr>
<tr>
<td>E. coli</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 diarrhea 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 two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible subjects had ≥2 episodes of HE associated with chronic liver disease in the previous 6 months.

A total of 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, 21-92 years), 81% <65 years of age, 61% were male and 86% White. At baseline, 67% of patients had a Conn score of 0 and 68% had an asterixis grade of 0. Patients had MELD scores of either ≤10 (27%) or 11 to 18 (64%) at baseline. No patients were enrolled with a MELD score of ≥25. Nine percent of the patients were Child-Pugh Class C. Lactulose was concomitantly used by 91% of the patients in each treatment arm of the study. Per the study protocol, patients were withdrawn from the study after experiencing a breakthrough HE episode. Other reasons for early study discontinuation included: adverse reactions (XIFAXAN 6%; placebo 4%), patient request to withdraw (XIFAXAN 4%; placebo 6%) and other (XIFAXAN 7%; placebo 5%).

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

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

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.
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. Trials 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 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 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 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 repeat treatment arm. 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.

Note: Open diamonds and open triangles represent censored subjects.

1 Event-free refers to non-occurrence of HE-related hospitalization.

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>
</table>
| Adequate Relief of IBS Symptoms               | XIFAXAN n=309 (41)             | Placebo n=314 (31)             | Treatment Difference (95% CI)
| Adequate Relief of IBS Symptoms               | 126 (10%)                      | 98 (10%)                       | 10% (2.1%, 17.1%)
| Adequate Relief of IBS Symptoms               | 128 (41)                       | 103 (32)                       | 8% (1.0%, 15.9%)

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

| Endpoint                                      | XIFAXAN n=309 (%) | Placebo n=314 (%) | Treatment Difference (95% CI)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>144 (47)</td>
<td>121 (39)</td>
<td>8% (0.3%, 15.9%)</td>
</tr>
<tr>
<td>Abdominal Pain Responders</td>
<td>159 (51)</td>
<td>132 (42)</td>
<td>9% (1.8%, 17.5%)</td>
</tr>
<tr>
<td>Stool Consistency Responders</td>
<td>244 (79)</td>
<td>212 (68)</td>
<td>11% (4.4%, 18.2%)</td>
</tr>
</tbody>
</table>

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

The exams examined a composite endpoint which defined responders by IBS-related cardinal symptoms. 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).

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.

**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.
Trial 3 - Results

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:

- ≥30% improvement from baseline in the weekly average abdominal pain score based on the daily question: “In regards to your specific IBS symptoms of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours?” Zero means you have no pain at all; Ten means the worst possible pain you can imagine”.

- at least a 50% 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.

Responders were then followed for recurrence of their IBS-related 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 2435 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 symptoms of 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 symptoms 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 during the 4 weeks following the first repeat treatment with XIFAXAN. The primary endpoint was symptom scores less severe than at study entry into the open-label phase, with XIFAXAN was 10 weeks (range 6 to 24 weeks).

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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Responder a, Abdominal Pain and Stool Consistency Responder b</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>

a Confidence intervals were derived based on CMH test adjusting for center and patients’ time to recurrence during maintenance phase.
b Primary endpoint

36 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%).