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.

• 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.

If you have IBS-D, you know it can control your life.

Break free from IBS-D

XIFAXAN provided up to 6 months of symptom relief with a 2-week treatment.*

*In a clinical trial: range of 6 to 24 weeks; average of 10 weeks. You can be retreated up to 2 times if symptoms come back. IBS-D = irritable bowel syndrome with diarrhea.

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

IBS-D is irritable bowel syndrome with diarrhea as the main symptom. It is a common disorder of the large intestine (colon) that affects about 16 million Americans and twice as many women as men.

IBS-D symptoms can be frequent and can vary widely from person to person. They include:

- **ABDOMINAL PAIN**
- **DIARRHEA**

  Loose, mushy, or watery stools and/or frequent bowel movements

What causes IBS-D?

IBS-D is thought to be caused by many different factors. Some potential factors include:

- Changes in the bacteria in your intestines
- Abnormal intestine contractions
- Food sensitivity

How to take XIFAXAN*:

- Take one 550 mg tablet 3 times a day for 2 weeks
- You can take with or without food
- Be sure to complete your 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)

- Talk to your healthcare provider before taking XIFAXAN if you have severe hepatic (liver) impairment, as this may cause increased effects of the medicine.
- Tell your healthcare provider if you are taking drugs called P-glycoprotein and/or OATPs inhibitors (such as cyclosporine) because using these drugs with XIFAXAN may lead to an increase in the amount of XIFAXAN absorbed by your body.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
What to expect while taking XIFAXAN

XIFAXAN is the only FDA-approved, 2-week treatment for IBS-D. In a clinical trial, XIFAXAN provided up to 6 months of relief from abdominal pain and diarrhea.*

- **2-week treatment**
- **Duration of relief (study average of 10 weeks)**

*In a clinical trial: range of 6 to 24 weeks; average of 10 weeks.

For patients whose symptoms did recur, symptoms were less severe after treatment with XIFAXAN. If your symptoms come back, talk to your doctor because you can be retreated up to 2 times.

**MOST COMMON SIDE EFFECTS**

In clinical studies, the most common side effects associated with XIFAXAN for IBS-D (≥2% and higher than placebo) were:

- Nausea (feeling sick to your stomach)
- An increase in liver enzymes

**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)

- 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.
- 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.

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 accompanying full Prescribing Information.

Most eligible1, commercially insured patients with coverage for XIFAXAN 550 mg may pay $0.

Applies to initial fills and refills. Activation is required.

1For most eligible, commercially insured patients. Maximum benefits and other restrictions apply. Visit www.xifaxan.com or call 1-855-250-3759 for full eligibility criteria, terms and conditions.
XIFAXAN® (rifaximin), tablets, for oral use
Initial U.S. Approval: 2004
To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE
XIFAXAN is indicated for:

1.1 Travelers’ Diarrhea
One 200 mg tablet 3 times a day for 3 days.

1.2 Hepatic Encephalopathy
One 550 mg tablet 2 times a day

1.3 Irritable Bowel Syndrome with Diarrhea
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.

Dosage Regimen

<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 antimicrobial agents, or any of the components of XIFAXAN (4)

WARNINGS AND PRECAUTIONS

• Travelers’ Diarrhea Not Caused by E. coli: XIFAXAN was not effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than E. coli. If diarrhea symptoms get worse or persist for more than 24 to 48 hours, discontinue XIFAXAN and consider alternative antibiotics (5.1)

• Clostridium difficile-Associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)

• Hepatic Impairment: Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment (5.4, 8.7)

• Concomitant P-glycoprotein (P-gp) inhibitors (e.g., cyclosporine): Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor is needed (5.5, 7.1)

ADVERSE REACTIONS

Most common adverse reactions:

• TD (≥2%): Headache (6.1)

• HE (≥10%): Peripheral edema, nausea, diziness, fatigue, and ascites (6.1)

• IBS-D (≥2%): ALT increased, nausea (6.1)

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (6.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 NURSING MOTHERS
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

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

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

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

2 DOSAGE AND ADMINISTRATION

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

2.2 Dosage for Hepatic Encephalopathy
The recommended dose of XIFAXAN is one 550 mg tablet taken orally two times a day.

2.3 Dosage for Irritable Bowel Syndrome with Diarrhea
The recommended dose of XIFAXAN is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

TREATMENT OF TRAVELERS’ DIARRHEA

• 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)

• 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)

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (6.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2018

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2.2 Dosage for Hepatic Encephalopathy
The recommended dose of XIFAXAN is one 550 mg tablet taken orally two times a day.

2.3 Dosage for Irritable Bowel Syndrome with Diarrhea
The recommended dose of XIFAXAN is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.
The patients were ≥65 years old, 61% were male, 86% were White, and 4% were Black.

The population studied had a mean age of 56 (range: 21 to 82) years; approximately 20% of patients were ≥65 years old, 53% were male and 84% were White, 11% were Hispanic.

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

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

- nausea (3% XIFAXAN, 2% placebo)

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

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

Less Common Adverse Reactions

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

- Musculoskeletal and connective tissue disorders: myalgia
- Infections and infestations: increased blood creatine phosphokinase
- Nervous system disorders: headache

Hepatic Encephalopathy

The data described below reflect exposure to XIFAXAN in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of XIFAXAN 550 mg taken twice a day for reducing the risk of hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-controlled clinical trial (n=140) and in a long term follow-up study (n=280). The population studied had a mean age of 56 (range: 21 to 82) years; approximately 20% of the patients were ≥65 years old, 56% were male, 86% were White, and 4% were Black.

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

Table 1: Most Common Adverse Reactions* in HE Trial

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>XIFAXAN Tablets 550 mg TWICE DAILY</th>
<th>Placebo n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>Number (%) of Patients</td>
<td></td>
</tr>
<tr>
<td>21 (15%)</td>
<td>13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 (14%)</td>
<td>21 (13%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 (13%)</td>
<td>13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (12%)</td>
<td>18 (11%)</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 (11%)</td>
<td>15 (9%)</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 (9%)</td>
<td>11 (7%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 (9%)</td>
<td>10 (6%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (9%)</td>
<td>13 (8%)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (7%)</td>
<td>8 (5%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (8%)</td>
<td>6 (4%)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (7%)</td>
<td>10 (6%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (6%)</td>
<td>8 (5%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (6%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (6%)</td>
<td>7 (4%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (6%)</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (5%)</td>
<td>6 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

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

Irritable Bowel Syndrome with Diarrhea

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

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

- Weight decrease

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

- ALT increased (XIFAXAN 2%, placebo 1%)
- Nausea (XIFAXAN 2%, placebo 1%)

Less Common Adverse Reactions

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

- Musculoskeletal and connective tissue disorders: myalgia
- Infections and infestations: increased blood creatine phosphokinase

6.2 Postmarketing Experience

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

Infections and Infestations

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

General

Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema, and anaphylaxis [see Adverse Reactions (6.2)].
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

8.1.1 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.

8.1.2 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

8.2.1 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.

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

8.7 Hepatic Impairment
Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC(0-24)) 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 dose adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), Clinical Studies (14.2)].

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

DESCRIPTION

![Chemical Structure of Rifaximin]

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 palmiostearate, hypromellose, microcrystalline cellulose, polyethylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.
Each 550 mg tablet contains colloidal silicon dioxide, glycerol palmiostearate, microcrystalline cellulose, polyethylene glycol/macrogol, polyvinyl alcohol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

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

12.2 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 mg/mL after a single dose and multiple doses of XIFAXAN 550 mg.

Traveler’s Diarrhea
Systemic absorption of XIFAXAN (200 mg three times daily) was evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, AUC(0-24) estimates were 5.95 ± 5.53 ng·h/mL on Day 1 and 7.93 ± 4.94 ng·h/mL on Day 3. XIFAXAN is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration [see Warnings and Precautions (5.1)].

Hepatic Encephalopathy
Mean rifaximin exposure (AUC(0-24)) in patients with a history of HE was approximately 12-fold higher than that observed in healthy subjects. Among patients with a history of HE, the mean AUC in patients with Child-Pugh Class C hepatic impairment was 2-fold higher than in patients with Child-Pugh Class A hepatic impairment [see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)].

Irritable Bowel Syndrome with Diarrhea
In patients with irritable bowel syndrome with diarrhea (IBS-D) treated with XIFAXAN 550 mg three times a day for 14 days, the median Tmax was 1 hour and mean Cmax and AUC were generally comparable with those in healthy subjects. After multiple doses, AUC was 1.65-fold higher than that on Day 1 in IBS-D patients (Table 2).
The systemic exposure of rifaximin was markedly elevated 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 primarily by CYP3A4. Rifaximin accounted for 18% of the radioactivity in plasma suggesting that the absorbed rifaximin undergoes extensive metabolism.

**Excretion**

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

**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 associated with a high variability and mean rifaximin exposure (AUCₜ) in patients with a history of HE was higher compared to those in healthy subjects. The mean AUCₜ in patients with hepatic impairment of Child-Pugh Class A, B, and C was 10-, 14-, and 21-fold higher, respectively, compared to that in healthy subjects (Table 3).

**Oral Contraceptives Containing Ethinyl Estradiol and Norgestimate**

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 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.

**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 enteropathogenic 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 Ct:CD (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg per day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for TD, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for HE, based on relative body surface area comparisons). There was no increase in tumors in Tg.rasH2 mice dosed orally with rifaximin for 26 weeks at 150 to 2000 mg/kg per day (doses equivalent to 1.2 to 16 times the recommended daily dose for TD and equivalent to 0.7 to 9 times the recommended daily dose for HE, based on relative body surface area comparisons).

Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA synthesis assay, or the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose of 600 mg per day for TD, and approximately 2.6 times the clinical dose of 1100 mg per day for HE, adjusted for body surface area).

14 CLINICAL STUDIES

14.1 Travelers’ Diarrhea

The efficacy of XIFAXAN given as 200 mg orally taken three times a day for 3 days was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled studies in adult subjects with travelers’ diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was Escherichia coli.

The clinical efficacy of XIFAXAN was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary endpoint was time to last unformed stool (TLUS) which was defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 4 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat (ITT) population of Study 1. The duration of diarrhea was significantly shorter in patients treated with XIFAXAN than in the placebo group. More patients treated with XIFAXAN were classified as clinical cures than were those in the placebo group.

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

<table>
<thead>
<tr>
<th></th>
<th>Median TLUS (hours)</th>
<th>Clinical cure, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XIFAXAN</td>
<td>32.5</td>
<td>99 (79)</td>
</tr>
<tr>
<td>Placebo</td>
<td>58.6</td>
<td>78 (60)</td>
</tr>
</tbody>
</table>

a Hazard Ratio (p-value <0.001)
b Difference in rates (p-value <0.01)

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stools and resolution of symptoms at 1 to 3 days following the end of treatment to identify enteric pathogens). There was no effect on microbiology eradication for HE. Based on relative body surface area comparisons.

XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of Shigella flexneri in the stool (1); five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

14.2 Hepatic Encephalopathy

The efficacy of XIFAXAN 550 mg taken orally twice a day was evaluated in a randomized, placebo-controlled, multi-center, 6-month trial of adult subjects from the U.S., Canada and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy. Eligible subjects had ≥2 episodes of HE associated with chronic liver disease in the previous 6 months.

A total of 298 subjects were randomized to receive either XIFAXAN (n=140) or placebo (n=159) in this study. Patients had a mean age of 56 years (range, 21-82 years), 811% < 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.

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 Curves1 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.

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 for 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.
Trials 1 and 2 - Results
Trials 1 and 2 included 1258 IBS-D patients (309 XIFAXAN, 314 placebo); (315 XIFAXAN, 320 placebo). The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. Adequate relief was defined as a response of “yes” to the following weekly Subject Global Assessment (SGA) question: “In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No].” Adequate relief of IBS symptoms was experienced more by patients receiving XIFAXAN than those receiving placebo during the month following 2 weeks of treatment (SGA-IBS Weekly Results: 41% vs. 31%, p=0.0125; 41% vs. 32%, p=0.0263 (See Table 6).

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>XIFAXAN n=309 n (%)</th>
<th>Placebo n=314 n (%)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Relief of IBS Symptomsb</td>
<td>126 (41)</td>
<td>98 (31)</td>
<td>10% (2.1%, 17.1%)</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 trials examined a composite endpoint which defined responders by IBS-related abdominal pain and stool consistency measures. Patients were monthly responders if they met both of the following criteria:
- experienced a ≥30% decrease from baseline in abdominal pain for ≥2 weeks during the month following 2 weeks of treatment
- had a weekly mean stool consistency score <4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment

More patients receiving XIFAXAN were monthly responders for abdominal pain and stool consistency in Trials 1 and 2 (see Table 7).

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 n (%)</th>
<th>Placebo n=314 n (%)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain and Stool Consistency Respondersb</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 composite endpoint for Trial 1 and 2 was <0.05 and <0.01, respectively.

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.

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* 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 (staining, urgency, or feeling of incomplete evacuation);
- Passage of mucus;
- Bloating or feeling of abdominal distension.

Trial 3 - Design
Trial 3 evaluated repeat treatment in adults with IBS-D meeting Rome III criteria** for up to 46 weeks. A total of 2579 patients meeting Rome II criteria for IBS were randomized to receive XIFAXAN 550 mg three times a day (n=636) 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 III Criteria: Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) at least 3 days/month in last 3 months associated with two or more of the following: 1. Improvement with defecation; 2. Onset associated with a change in frequency of stool; 3. Onset associated with a change in form (appearance) of stool.

The 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.
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 2438 evaluable patients who responded to initial treatment with improvement in abdominal pain and stool consistency. The response rate for each IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2 (see Table 7). A total of 636 patients subsequently had sign and 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 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. 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%).

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