

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) tablets, for oral use  
Initial U.S. Approval: 2004

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

### INDICATIONS AND USAGE

XIFAXAN is a rifamycin antibacterial indicated for:

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

### Limitations of Use

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

### DOSAGE AND ADMINISTRATION

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

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

### DOSAGE FORMS AND STRENGTHS

200 mg and 550 mg tablets (3)

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### 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, dizziness, fatigue, and ascites (6.1)
- IBS-D (≥2%): ALT increased, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

Warfarin: Monitor INR and prothrombin time; dose adjustment of warfarin may be needed to maintain target INR range. (7.2)

### USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (8.1)

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Revised: 10/2022

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## 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 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. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. 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 adults and pediatric patients 12 years of age and older.

##### *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 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage for Travelers' Diarrhea

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

#### 2.2 Dosage for Hepatic Encephalopathy

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

#### 2.3 Dosage for Irritable Bowel Syndrome with Diarrhea

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

#### 2.4 Administration

XIFAXAN can be taken with or without food [see *Clinical Pharmacology (12.3)*].

### 3 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

The following clinically significant adverse reactions are described elsewhere in labeling:

- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.2)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Travelers' Diarrhea

The safety of XIFAXAN 200 mg taken three times a day was evaluated in patients with travelers' diarrhea consisting of 320 patients in two placebo-controlled clinical trials with 95% of patients receiving three or four days of treatment with XIFAXAN. The population studied had a mean age of 31.3 (18-79) years of which approximately 3% were  $\geq 65$  years old, 53% were male and 84% were White, 11% were Hispanic.

Discontinuations due to adverse reactions occurred in 0.4% of patients. The adverse reactions leading to discontinuation were taste loss, dysentery, weight decrease, anorexia, nausea and nasal passage irritation.

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

- headache (10% XIFAXAN, 9% placebo)

#### Hepatic Encephalopathy

The data described below reflect exposure to XIFAXAN in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of XIFAXAN 550 mg taken two times a day for reducing the risk of overt hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-controlled clinical trial (n=140) and in a long-term follow-up study (n=280). The population studied had a mean age of 56 (range: 21 to 82) years; approximately 20% of the patients were  $\geq 65$  years old, 61% were male, 86% were White, and 4% were Black. Ninety-one percent of patients in the trial were taking lactulose concomitantly. The most common adverse reactions that occurred at an incidence  $\geq 5\%$  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**

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN Tablets 550 mg TWICE DAILY n=140	Placebo n=159
Peripheral edema	21 (15%)	13 (8%)
Nausea	20 (14%)	21 (13%)
Dizziness	18 (13%)	13 (8%)
Fatigue	17 (12%)	18 (11%)
Ascites	16 (11%)	15 (9%)
Muscle spasms	13 (9%)	11 (7%)
Pruritus	13 (9%)	10 (6%)
Abdominal pain	12 (9%)	13 (8%)
Anemia	11 (8%)	6 (4%)
Depression	10 (7%)	8 (5%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (3%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

\* Reported in  $\geq 5\%$  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  $\geq 65$  years old, 72% were female, 88% were White, 9% were Black, and 12% were Hispanic.

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

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

#### Less Common Adverse Reactions

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

*Hepatobiliary disorders:* Clostridium colitis

*Investigations:* Increased blood creatine phosphokinase

*Musculoskeletal and connective tissue disorders:* Myalgia

## 6.2 Postmarketing Experience

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

### Infections and Infestations

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

### Hypersensitivity Reactions

Exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.

### Musculoskeletal and Connective Tissue Disorders

Cases of rhabdomyolysis have been reported in patients with cirrhosis, with and without concomitant statin use.

### Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with the use of rifaximin in patients with cirrhosis. Discontinue rifaximin at the first signs or symptoms of a severe cutaneous adverse reaction or other signs of hypersensitivity and conduct a clinical evaluation.

## 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 (5.5)*, *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

















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

	XIFAXAN	Placebo
Overall	48/70 (69)	41/61 (67)
<i>E. coli</i>	38/53 (72)	40/54 (74)

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 (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the subjects treated with XIFAXAN who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated open-label, pharmacokinetic study of oral XIFAXAN 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with XIFAXAN. Although this open-label challenge trial was not adequate to assess the effectiveness of XIFAXAN in the treatment of shigellosis, the following observations were noted: eight subjects received rescue treatment with ciprofloxacin either because of lack of response to XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* 2a 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

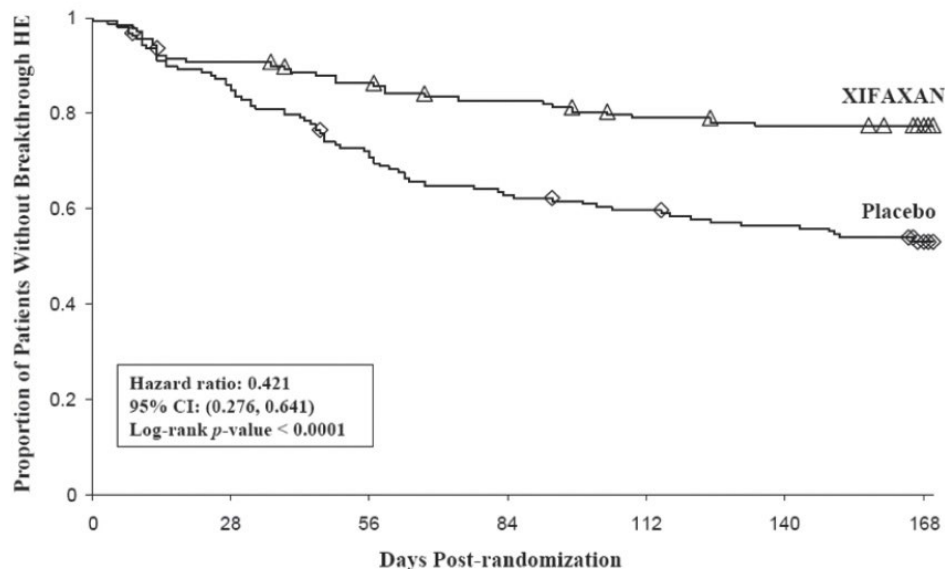
The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada, and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible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

A total of 299 subjects were randomized to receive either XIFAXAN (n=140) or placebo (n=159) in this study. Patients had a mean age of 56 years (range, 21-82 years), 81% <65 years of age, 61% were male and 86% White. At baseline, 67% of patients had a Conn score of 0 and 68% had an asterixis grade of 0. Patients had MELD scores of either  $\leq 10$  (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  $\geq 2$ . 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<sup>1</sup> in HE Study  
(Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170)  
(ITT Population)**



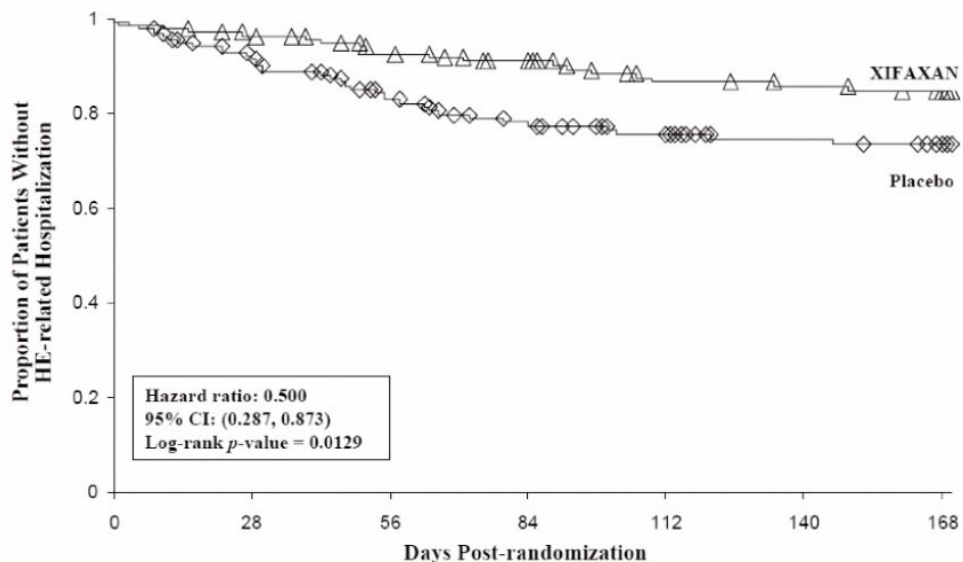
Note: Open diamonds and open triangles represent censored subjects.

<sup>1</sup> 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=31), and those without concomitant lactulose use (n=26).

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

**Figure 2: Kaplan-Meier Event-Free Curves<sup>1</sup> 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.

<sup>1</sup> 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 1,258 patients meeting Rome II criteria for IBS\* were randomized to receive XIFAXAN 550 mg three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period. The Rome II criteria further categorizes IBS patients into 3 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or alternating IBS (bowel habits alternating between diarrhea and constipation). Patients with both IBS-D and alternating IBS were included in Trials 1 and 2. XIFAXAN is recommended for use in patients with IBS-D.

\*Rome II Criteria: *At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:* 1. Relieved with defecation; *and/or* 2. Onset associated with a change in frequency of stool; *and/or* 3. Onset associated with a change in form (appearance) of stool.

*Symptoms that Cumulatively Support the Diagnosis of Irritable Bowel Syndrome:*

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

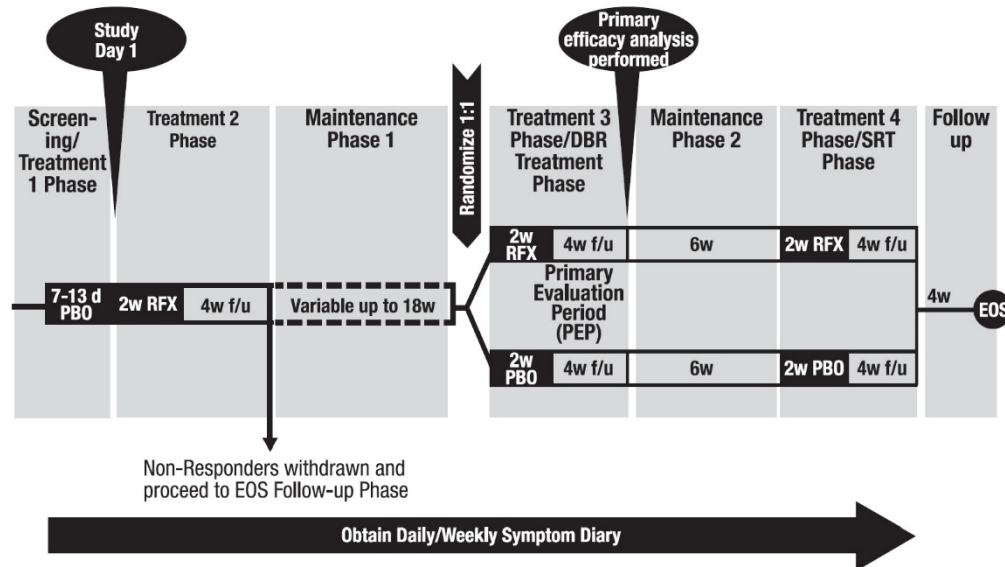
#### Trial 3 - Design

Trial 3 evaluated repeat treatment in adults with IBS-D meeting Rome III criteria\*\* for up to 46 weeks. A total of 2,579 patients were enrolled to receive open-label XIFAXAN for 14 days. Of 2,438 evaluable patients, 1,074 (44%) responded to initial treatment and were evaluated over 22 weeks for continued response or recurrence of IBS-symptoms. A total of



636 patients had symptom recurrence and were randomized into the double-blind phase of the study. These patients were scheduled to receive XIFAXAN 550 mg three times a day (n=328) or placebo (n=308) for two additional 14-day repeat treatment courses separated by 10 weeks. See Figure 3.

**Figure 3: Trial 3 Study Design**



The IBS-D population from the three studies had mean age of 47 (range: 18 to 88) years of which approximately 11% of patients were  $\geq 65$  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.

Trials 1 and 2 - Results

Trials 1 and 2 included 1,258 IBS-D patients (309 XIFAXAN, 314 placebo); (315 XIFAXAN, 320 placebo). The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. Adequate relief was defined as a response of “yes” to the following weekly Subject Global Assessment (SGA) question: *“In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No].”*

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

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

Endpoint	Trial 1		
	XIFAXAN n=309 n (%)	Placebo n=314 n (%)	Treatment Difference (95% CI <sup>a</sup> )
Adequate Relief of IBS Symptoms <sup>b</sup>	126 (41)	98 (31)	10% (2.1%, 17.1%)

Endpoint	Trial 2		
	XIFAXAN n=315 n (%)	Placebo n=320 n (%)	Treatment Difference (95% CI <sup>a</sup> )
Adequate Relief of IBS Symptoms <sup>b</sup>	128 (41)	103 (32)	8% (1.0%, 15.9%)

<sup>a</sup> Confidence Interval

<sup>b</sup> 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  $\geq 30\%$  decrease from baseline in abdominal pain for  $\geq 2$  weeks during the month following 2 weeks of treatment
- had a weekly mean stool consistency score <4 (loose stool) for  $\geq 2$  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**

Endpoint	Trial 1		
	XIFAXAN n=309 n (%)	Placebo n=314 n (%)	Treatment Difference (95% CI <sup>a</sup> )
Abdominal Pain and Stool Consistency Responders <sup>b</sup>	144 (47)	121 (39)	8% (0.3%, 15.9%)
Abdominal Pain Responders	159 (51)	132 (42)	9% (1.8%, 17.5%)
Stool Consistency Responders	244 (79)	212 (68)	11% (4.4%, 18.2%)

Endpoint	Trial 2		
	XIFAXAN n=315 n (%)	Placebo n=320 n (%)	Treatment Difference (95% CI <sup>a</sup> )
Abdominal Pain and Stool Consistency Responders <sup>b</sup>	147 (47)	116 (36)	11% (2.7%, 18.0%)
Abdominal Pain Responders	165 (52)	138 (43)	9% (1.5%, 17.0%)
Stool Consistency Responders	233 (74)	206 (64)	10% (2.3%, 16.7%)

<sup>a</sup> Confidence Interval

<sup>b</sup> The *p*-value for the composite endpoint for Trial 1 and 2 was <0.05 and <0.01, respectively

### Trial 3 - Results

In TARGET 3, 2,579 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:

- $\geq 30\%$  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 1,074 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, 1,257 of 2,579 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 1,074 (44%) of 2,438 evaluable patients who responded to initial treatment with improvement in abdominal pain *and* stool consistency. The response rate for each IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2 (see Table 7). A total of 636 patients subsequently had sign and symptom recurrence and were randomized to the repeat treatment phase. The median time to recurrence for patients who experienced initial response during the open-label phase with XIFAXAN was 10 weeks (range 6 to 24 weeks).

The XIFAXAN (rifaximin) and placebo treatment groups had similar baseline IBS symptom scores at the time of recurrence and randomization to the double-blind phase, but symptom scores were less severe than at study entry into the open-label phase.

Patients were deemed to have recurrent signs and symptoms by the following criteria: a return of abdominal pain or lack of stool consistency for at least 3 weeks during a 4-week follow-up period. The primary endpoint in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain *and* stool consistency as defined above during the 4 weeks following the first repeat treatment with XIFAXAN. The primary analysis was performed using the worst case analysis method where patients with <4 days of diary entries in a given week are considered as non-responders for that week.

More patients receiving XIFAXAN were monthly responders for abdominal pain *and* stool consistency in the primary analysis in Trial 3 (see Table 8).

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

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

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

<sup>b</sup> Primary endpoint

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

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

The 200 mg tablet is a pink-colored, round, biconvex tablet with “Sx” debossed on one side and plain on the other. It is available in the following presentation:

- NDC 65649-301-03, bottles of 30 tablets

The 550 mg tablet is a pink-colored, oval, biconvex tablet with “rfx” debossed on one side and plain on the other. It is available in the following presentations:

- NDC 65649-303-02, bottles of 60 tablets
- NDC 65649-303-03, carton of 60 tablets, Unit Dose

### Storage

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

## 17 PATIENT COUNSELING INFORMATION

### Persistent Diarrhea

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

### *Clostridium difficile*-Associated Diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon which may lead to *C. difficile*. Patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If diarrhea occurs after therapy or does not improve or worsens during therapy, advise patients to contact a physician as soon as possible [*see Warnings and Precautions (5.2)*].

### Administration with Food

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

### Antibacterial Resistance

Counsel patients that antibacterial drugs including XIFAXAN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When XIFAXAN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by XIFAXAN or other antibacterial drugs in the future [*see Warnings and Precautions (5.3)*].

### **Distributed by:**

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