A Medicine Proven to Significantly Reduce the Risk of Overt Hepatic Encephalopathy (HE) Recurrence and HE-Related Hospitalizations in Adults

Introduction

Chronic liver disease and cirrhosis—which afflict approximately 5.5 million Americans—play a substantial role in rising health care costs in the United States.1,2

Cirrhosis—the end result complication of chronic injury to the liver—often leads to additional serious complications, such as portal hypertension and hepatic insufficiency.3 Patients with portal hypertension and its hemodynamic consequences are predisposed to complications such as gastrointestinal (GI)/variceal bleeding, ascites, renal injury/dysfunction, and circulatory failure.3 Meanwhile, hepatic insufficiency can alter drug metabolism; it often precipitates hepatic encephalopathy (HE).3,4

Hepatic encephalopathy is one of the most common complications of cirrhosis, and places a significant burden on patients and the health care system,1,2 causing:

• increased morbidity and mortality1;
• high rates of hospitalizations and associated costs5,6;
• high readmission rates due to high risk for recurrence.7

In fact, the risk of readmission for HE is higher than it is for any other complication of cirrhosis.7

Diagnosing and treating HE early may lead to improved clinical and economic outcomes. Guideline-driven treatment includes

INDICATION

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

IMPORTANT SAFETY INFORMATION

• XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

Please see Important Safety Information on pages 1-6.
Please see the full Prescribing Information on pages 11-16.
intervening with recommended first-line therapy as quickly as possible, along with secondary prophylaxis to reduce the risk of recurrent HE.

Guidelines recommend using rifaximin (Xifaxan) for secondary prophylaxis after a patient has suffered an overt HE recurrence while on lactulose alone. Rifaximin was evaluated in a phase 3, randomized, placebo-controlled, double-blind, multicenter, multinational trial, where it significantly reduced the risk of overt HE recurrence, and reduced HE-related hospitalizations (See Figures 1-3 and Tables 2-3).

**Overview of Hepatic Encephalopathy**

Hepatic encephalopathy is a cerebral abnormality caused by liver insufficiency and/or portosystemic shunting. It is characterized by an array of neuropsychiatric impairments and neuromuscular irregularities that lead to significant morbidity and mortality, and has a substantial impact on health care resource use. Most patients with liver disease are likely to develop HE to some extent. Moreover, it is one of the chief complications of end-stage liver disease, and thus a major issue for patients with cirrhosis. The neurological and psychiatric abnormalities that manifest as a result of HE can range from subclinical alterations to coma.

The 30-day mortality in patients with the most severe grades of HE is of particular concern. In fact, disease severity can predict 30-day mortality in cirrhosis independent of other end-organ failures according to a study involving 1560 individuals. Investigators recorded the presence and grade of HE at admission as well as the maximum grade during hospitalization. They found that:

- the 30-day mortality rates for hospitalized patients with the highest disease severity was 38%, compared with 8% in those with low disease severity and 7% where no HE was present;
- 9% of the study population had the most severe HE, and they accounted for the majority of the deaths;
- most of these patients had severe HE at admission.

The authors concluded that prompt medical attention is important before HE becomes severe, and that clinicians should seek to prevent severe HE while the patient is hospitalized.

**Grades of HE and Patient Presentation**

HE is either covert or overt, and progresses in severity along 5 stages: minimal, followed by Grades I through IV (Table 1). Minimal disease requires specialized psycho-

<table>
<thead>
<tr>
<th>TABLE 1. Stages of HE⁸</th>
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<tr>
<td><strong>Covert HE</strong></td>
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<tr>
<td>Minimal</td>
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<tr>
<td>No observable symptoms</td>
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<td>Detectable only by psychometric testing</td>
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Abbreviation: HE, hepatic encephalopathy.

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**IMPORTANT SAFETY INFORMATION – Xifaxan 550 mg in HE (cont’d)**

- *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. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
metric testing to identify slight changes in neuropsychological function. From there HE progresses to Grade I, where patients show mild neurologic changes, including euphoria or anxiety, as well as difficulty adding and subtracting. Sleep and attention issues are also seen. Patients with Grade II disease exhibit pronounced personality and behavioral changes; they seem to be lethargic, apathetic, and disoriented about time, and asterixis may be observed. By the time patients progress to Grade III, lethargy evolves into somnolence or semi-stupor that responds to stimuli. Additionally, they are generally confused and very disoriented, and their behavior can be bizarre. With Grade IV disease, patients become comatose.

Incidence and Prevalence
The majority of patients with liver disease will develop some form of HE. Overt disease occurs in up to 45% of people with cirrhosis during their disease course, and patients who reach this stage are very likely to experience recurring episodes. The cumulative risk for recurrence within 1 year of the initial episode is 40%. Moreover, patients who experience recurrence have an additional 40% cumulative risk of yet another recurrence within 6 months, despite treatment with lactulose.

Burden of HE
The prevalence of HE in patients with cirrhosis, its significant detrimental health impact, and the likelihood of recurrence are draining the resources of patients and society, leading to dramatic personal, financial, and health care resource burdens. A cross-sectional study involving 104 individuals with cirrhosis showed the financial burden of the condition to be substantial. Sixty-three percent of patients felt that their financial status had decreased after diagnosis, and 44% stopped working. HE is a common cause of hospitalizations in patients with cirrhosis, and is likely to be under-recognized in both inpatient and outpatient settings. From 2005 to 2009, there was a more than 50% increase in overall total charges for HE hospitalizations, increasing from about $4.6 billion in 2005 to more than $7 billion in 2009. The increase in total national cost for HE during the same time was 24% (adjusted for inflation). HE accounts for nearly 23,000 hospitalizations with an average stay of 8.5 days and average cost of more than $64,000.

Patients with overt HE experience negative clinical outcomes, reduced quality of life, and social and occupational limitations, including permanent disability and difficulty driving. In a study involving nearly 99 individuals, driving instructors determined that patients with overt or minimal HE (n=51) were less fit to drive compared with age-matched controls without the disease (n=48). Three-fourths in the control group were fit to drive, vs less than half of those with minimal HE and just 4 in every 10 with overt disease. Cognitive deficits and prolonged reaction times were primarily to blame. Additionally, those with minimal HE had issues tied to attention deficits.

Overt HE’s impact extends beyond patients to their families and caregivers, who face financial stress, time burdens, health consequences, and mood problems. Mild to severe depression and anxiety are seen in people who care for patients with overt HE. Overt HE also places considerable stress on the health care system, costing the United States approximately $7.2 billion each year.

HE and Readmissions
Readmission rates for HE are high, and in fact are the highest among any complications of cirrhosis. Under the Affordable Care Act, the Centers for Medicare & Medicaid Services is authorized to reduce payments to acute care hospitals with excess readmissions for core conditions such as acute myocardial infarction, heart failure, chronic obstructive pulmonary disease.

Important Safety Information – Xifaxan 550 mg in HE (cont’d)
• There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering XIFAXAN to these patients.
pneumonia, and others. So even though HE itself is not currently identified as a core condition, patients with the disorder usually present with a core measure comorbidity. Moreover, core measure conditions plus a comorbid diagnosis of cirrhosis or HE negatively impacts clinical outcomes and health care resource use, increasing 30-day readmission rates, average length of stay, and mortality rates.

A large study analyzed approximately 120,000 individuals with cirrhosis admitted to hospitals in California, Florida, Massachusetts, and New York in 2011. The overall 30- and 90-day readmissions rates for HE were 13% and 21%, respectively.

Another study involving more than 1000 individuals from The North American Consortium for the Study of End-Stage Liver Disease revealed that 53% experienced at least 1 readmission with 90 days, and that the leading reasons included HE and renal/metabolic issues. Moreover, 4 in every 10 who were readmitted had more than 1 readmission (139 had 2 readmissions; 54 had 3; and 26 had 4).

**Early Identification and Management**

Early diagnosis and treatment of HE is important to support good clinical and economic outcomes. All patients with cirrhosis should be routinely assessed for HE symptoms, as this will help identify and manage HE more quickly. If overt HE is observed, the patient should be referred to a liver unit immediately for prompt treatment initiation. For any episode of overt HE, the American Association for the Study of Liver Disease/European Association for the Study of the Liver (AASLD/EASL) guidelines recommend that clinicians:

- initiate care for patients with altered consciousness;
- treat alternative causes of altered mental status;
- identify and correct precipitating factors;
- commence initial treatment with lactulose.

The AASLD/EASL guidelines for the treatment of overt HE raise questions about lactulose monotherapy’s ability to reduce the risk of overt HE recurrence, since chance of recurrence remains high (40%) even during such therapy. Additionally, lactulose overuse can lead to complications, such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation.

Lactulose overuse might even encourage HE. In a retrospective analysis involving 137 patients from a liver transplant center who received lactulose therapy for HE, three-fourths experienced HE recurrence an average of 9 months after the initial episode. Thirty-nine of the recurrences were due to nonadherence.

Therefore, secondary prophylaxis is critical to reduce the risk of recurrence in patients recovering from their initial episode. Physicians should start secondary treatment after the initial episode, and if needed seek advice from a gastroenterologist or liver disease specialist. Guidelines recommend using rifaximin for this purpose.

A 2016 Consensus Statement on management of HE additionally supports the AASLD/EASL guidelines, highlighting that prompt initiation of appropriate management can reduce the duration of admission and reduce the risk of subsequent readmission. Moreover, use of rifaximin with lactulose was shown to reduce the risk of a breakthrough episode of HE over 6 months in patients who had 2 or more overt HE episodes within the previous 6 months.

**Rifaximin for HE Management**

Rifaximin is indicated for reduction in risk of overt HE recurrence in adults. The recommended dose for overt HE is one 550 mg tablet taken orally twice a day.

Rifaximin—a nonaminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV—is an oral, broad-spectrum, rifamycin antibiotic that targets the gut. A structural analog of rifampin, it acts by binding to the beta-subunit of bacterial

**IMPORTANT SAFETY INFORMATION – XIFAXAN 550 MG IN HE (CONT’D)**

- 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 P-glycoprotein (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.
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. The systemic exposure of rifaximin was elevated in patients with more severe hepatic impairment compared with healthy subjects.

**Study Design**
Rifaximin 550 mg twice daily was evaluated in a phase 3, randomized, placebo-controlled, double-blind, multicenter, multinational trial with an open-label extension that included adult patients from the United States, Canada, and Russia. Investigators assessed efficacy and safety for maintenance of remission in patients considered in remission but with a recent history of recurrent overt HE, with a score of ≤25 on the Model for End-Stage Liver Disease scale. Inclusion criteria were the occurrence of ≥2 prior episodes of overt HE associated with hepatic cirrhosis within 6 months of screening and remission at the time of screening. Patients expecting liver transplant within 1 month after screening were excluded, as were those with active spontaneous bacterial peritonitis, intercurrent infection, GI hemorrhage, transjugular intrahepatic portosystemic shunt (TIPS) placement within 3 months of screening, chronic renal or respiratory insufficiency, anemia, or electrolyte abnormality.

The trial included 299 participants from 70 sites in 3 countries, including the United States (n=205), Canada (n=14), and Russia (n=80). They ranged between 21 and 82 years of age, with an average age of 56 years. Eight out of 10 were younger than age 65 years (mean age, 56 years [range, 21-82 years]). Six in 10 were male, and 86% were white. Roughly two-thirds (67%) showed no sign of personality or behavioral abnormalities (Conn score of 0), and 68% had no tremors (asterixis grade of 0). Sixty-four percent of patients had a MELD score of 11 to 18, and 27% had a score of 10 or lower. No patients had MELD score exceeding 25. The range for MELD scores is 6 to 40, with higher numbers indicating more severe disease. Nine percent of patients were Child-Pugh Class C.

Participants were randomized 1:1 to receive rifaximin 550 mg twice daily (n=140) or placebo (n=159) for 6 months (Figure 1). Lactulose was allowed throughout the trial, and 91% of patients in each treatment group received concomitant lactulose therapy. All patients received at least 1 dose of the study drug and underwent at least 1 safety assessment. Patients were withdrawn from the study after experiencing a breakthrough episode of overt HE. Other reasons for early discontinuation included:

- adverse reactions: 6% and 4% in the rifaximin and placebo groups, respectively;
- patient request to withdraw: 4% and 6%, respectively;
- other reasons: 7% and 5%, respectively.

The primary endpoint was the time to first breakthrough episode of overt HE, defined as either:

- a marked deterioration in neurologic function and an increase in Conn score to ≥2; or
- if the baseline Conn score was 0, an increase to 1 and a 1-point increase in the asterixis grade.

The secondary endpoint was the time to first HE-related hospitalization, defined as hospitalization due to the disorder, or during which an overt HE episode occurred.

**Reduced Risk of Breakthrough Overt HE as Well as Fewer HE-Related Hospitalizations**
Rifaximin 550 mg significantly reduced the risk of overt HE recurrence by 58% compared with placebo over 6-months (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.28-0.64; P<0.001) (Figure 2). Breakthrough episodes of HE occurred in 22% of patients (31/140) who
received the study drug and 46% of patients (73/159) who received placebo at 6 months. Breakthrough overt HE episode was defined as a marked deterioration in neurologic 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.

Rifaximin 550 mg also led to fewer hospitalizations, significantly reducing the risk of HE-related admissions by 50% compared with placebo (HR, 0.50; 95% CI, 0.29-0.87; P=0.0129) (Figure 3). HE-related hospitalizations were observed in 14% of patients (19/140) who received the study drug and 23% of patients (36/159) who received placebo at 6 months. HE-related hospitalizations were defined as hospitalizations directly resulting from HE, or hospitalizations complicated by HE.

**Adverse Events**

The incidence of adverse events was similar in the both groups, with 80% of patients in each experiencing at least 1 such event (Table 2). The frequency of the more common serious adverse events (≥2% of patients in either treatment group) was also similar between the 2 groups. The following adverse events occurred in ≥10% of patients in both arms: **Peripheral Edema**, **Nausea**, **Dizziness**, **Fatigue**, and **Ascites**.

**FIGURE 1. Study Design**

*The open-label maintenance study was 24-months long and included patients with HE who participated in the randomized, controlled trial and new patients enrolled from March 2007 to December 2010.

**Abbreviation:** BID, twice a day.

**Inclusion criteria:** Occurrence of ≥2 prior episodes of overt HE associated with hepatic cirrhosis within 6 months of screening and remission at the time of screening.10

**Exclusion criteria:** Expectation of liver transplantation within 1 month after screening, active spontaneous bacterial peritonitis, intercurrent infection, gastrointestinal hemorrhage, transjugular intrahepatic portosystemic shunt (TIPS) placement within 3 months of screening, chronic renal or respiratory insufficiency, anemia, or electrolyte abnormality.10

**IMPORTANT SAFETY INFORMATION – XIFAXAN 550 MG IN HE (CONT’D)**

- In a clinical study, the most common adverse reactions for XIFAXAN in HE (≥ 10%) were peripheral edema (15%), nausea (14%), dizziness (13%), fatigue (12%), and ascites (11%).
A Medicine Proven to Significantly Reduce the Risk of Overt Hepatic Encephalopathy (HE) Recurrence and HE-Related Hospitalizations in Adults

Breakthrough overt HE episode was defined as a marked deterioration in neurologic function and an increase in 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. 91% of patients across both arms of the trial concomitantly used lactulose.

Abbreviations: CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio.

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.
Indication

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

Important Safety Information

- XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.
- 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. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.
- There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering XIFAXAN to these patients.
- 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 P-glycoprotein (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.
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.
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Conclusion

Symptoms of overt HE are debilitating and decrease the ability for self-care, which can lead to poor nutrition,
treatment nonadherence, severe symptoms, frequent hospitalizations, and decreased life quality.\textsuperscript{10} Rifaximin was proven to significantly reduce the risk of overt HE recurrences and HE-related hospitalizations.\textsuperscript{10}

References


XIFAXAN® (rifaximin) tablets, for oral use

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**INDICATIONS AND USAGE**

XIFAXAN is a rifamycin antibacterial indicated for:

- **Treatment of travelers’ diarrhea (TD) caused by noninvasive strains of Escherichia coli in adult and pediatric patients 12 years of age and older.**
- **Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.**

XIFAXAN® (rifaximin) tablets, for oral use

WHERE TO BUY

XIFAXAN® (rifaximin) tablets are available in the following strengths:

- **200 mg** – a round tablet debossed with “Sx” on one side.
- **550 mg** – a round tablet debossed with “Sx” on one side.

**CONTRAINdications**

- **Hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of XIFAXAN**

**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 due to pathogens other than E. coli.
- **Clostridium difficile-Associated Diarrhea:** Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy.
- **Hepatic Impairment:** Use with caution in patients with severe (Child-Pugh Class C) hepatic impairment.
- **Concomitant P-glycoprotein inhibitor:** Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor is needed.

**ADVERSE REACTIONS**

Most common adverse reactions:

- **TD:** Headache
- **HE:** Peripheral edema, nausea, dizziness, fatigue, and ascites
- **IBS-D:** ALT increased, nausea

**DOSAGE FORMS AND STRENGTHS**

- **200 mg and 550 mg tablets**
- **550 mg tablet**

**Dosage and Administration**

**TD (≥12 years old):**
- **One 550 mg tablet 2 times a day for 3 days.**

**HE (≥18 years old):**
- **One 550 mg tablet 2 times a day.**

**IBS-D (≥12 years old):**
- **One 550 mg tablet 3 times a day for 14 days.**

**Full Prescribing Information: Contents**

1. **INDICATIONS AND USAGE**

   **1.1 Travelers’ Diarrhea**

2. **DOSE AND ADMINISTRATION**

   **2.1 Dosage for Travelers’ Diarrhea**

3. **DOSE FORMS AND STRENGTHS**

4. **CONTRAINDICATIONS**

5. **WARNINGS AND PRECAUTIONS**

6. **ADVERSE REACTIONS**

7. **DRUG INTERACTIONS**

8. **USE IN SPECIFIC POPULATIONS**

9. **HOW SUPPLIED/STORAGE AND HANDLING**

10. **PATIENT COUNSELING INFORMATION**

**Warnings and Precautions**

- **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.
- **HE:** Do not use in patients with severe (Child-Pugh Class C) hepatic impairment.
- **IBS-D:** Do not use in patients not using lactulose concomitantly.

**Dosage and Administration**

- **TD:** One 550 mg tablet 2 times a day for 3 days.

- **HE:** One 550 mg tablet 2 times a day.

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5.2 Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of all antibiotic 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, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

5.3 Development of Drug-Resistant Bacteria

Prescribing XIFAXAN for travelers’ diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.4 Severe (Child-Pugh Class C) Hepatic Impairment

There is increased systemic exposure in patients with severe hepatic impairment. The clinical trials were limited to patients with MELD scores <25. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh Class C) [see Use in Specific Populations (8.7), Clinical Studies (14.2)].

5.5 Concomitant use with P-glycoprotein inhibitors

Concomitant administration of drugs that are P-glycoprotein inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Rifaximin should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-glycoprotein inhibitors may further increase the systemic exposure to rifaximin [see Drug Interactions (7.2), Pharmacokinetics (12.3)].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XIFAXAN. Since 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.

6.3 Use in Specific Populations

8 Pregnancy

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 0.3 to 5 times and 0.7 to 33 times, respectively, of the reported human doses of 600 mg to 1650 mg per day. In rabbits, oral, ocular and maxillofacial, cardiac, and minor spine malformations were observed. Occult 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.

8.2 Lactation

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 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 Pediatric Use

8.5 Geriatric Use

The data described below reflect exposure to XIFAXAN in 328 patients who received 1 open-label treatment (n=140) and in a long-term follow-up study (n=288). The population studied had a mean age of 31.3 (18-79) years of which approximately 3% were <65 years old, 53% were male and 48% were White, 11% were Hispanic.

6.4 Infections and Infestations

8.8 Postmarketing Experience

These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae.

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 (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 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 vertebrae.
glycol/macrogol, polyvinyl alcohol, red iron oxide, sodium starch disodium edetate, glycerol palmitostearate, hypromellose, and contain 200 mg or 550 mg of rifaximin.

785.9. The chemical structure is represented below:

In healthy subjects, the mean time to reach peak concentration of rifampin. The chemical name for rifaximin is (2S,7R)-2-[3-(2-aminoethyl)benzimidazole-1,15(2H)-dione,24-acetate. The empirical formula is C43H51N3O11 and its molecular weight is 683.84.

In vitro, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when XIFAXAN was administered.

Effect of food on healthy subjects. A high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC of rifaximin by 2-fold but did not significantly affect Cmax.

Distribution

Rifaximin is moderately bound to human plasma proteins. In vivo, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when XIFAXAN was administered.

Elimination

The mean half-life of rifaximin in healthy subjects at steady-state was 5.6 hours and was 6 hours in IBS-D patients.

Metabolism:

In an in vitro study rifaximin was metabolized mainly by CYP3A4. Rifaximin accounted for 18% of radioactivity in plasma suggesting that the absorbed rifaximin undergoes extensive metabolism.

Excretion

In a mass balance study, after administration of 400 mg rifaximin orally to healthy volunteers, of the 96.94% bioequivalent was recovered. Of the administered activity was recovered in feces mostly as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.

Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was detected in the bile after administration of XIFAXAN 550 mg three times a day for 14 days, the median Tmax was 1 hour and mean Cmax and AUC∞ in patients with hepatic impairment were generally comparable with those in healthy subjects. After multiple doses, AUC increased 1.62-fold higher than that on Day 1 in IBS-D patients (Table 2).

Table 2. Mean (± SD) Pharmacokinetic Parameters of Rifaximin Following XIFAXAN 550 mg Three Times a Day in IBS-D Patients and Healthy Subjects

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng•h/mL)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-State</td>
<td>24</td>
<td>4.04 (1.38)</td>
<td>10.4 (7.52)</td>
<td>1.83 (0.57)</td>
</tr>
<tr>
<td>IBSD Patients</td>
<td>24</td>
<td>5.63 (4.28)</td>
<td>16.0 (10.55)</td>
<td>3.14 (1.71)</td>
</tr>
<tr>
<td>Healthy Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady-State</td>
<td>14</td>
<td>7.05 (3.51)</td>
<td>16.0 (10.55)</td>
<td>3.14 (1.71)</td>
</tr>
<tr>
<td>IBSD Patients</td>
<td>14</td>
<td>8.78 (4.97)</td>
<td>24.6 (18.62)</td>
<td>4.0 (2.48)</td>
</tr>
</tbody>
</table>

\[ \text{Median (range)} \]

Food Effect in Healthy Subjects

A high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC of rifaximin by 2-fold but did not significantly affect Cmax.

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

<table>
<thead>
<tr>
<th>Child-Pugh Class</th>
<th>AUC (ng•h/mL)</th>
<th>Cmax (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=12)</td>
<td>1.32 (0.87)</td>
<td>3.4 (1.6)</td>
</tr>
<tr>
<td>B (n=13)</td>
<td>2.54 (1.76)</td>
<td>5.1 (2.0)</td>
</tr>
<tr>
<td>C (n=6)</td>
<td>4.0 (2.2)</td>
<td>7.0 (3.5)</td>
</tr>
</tbody>
</table>

\[ \text{Cross-study comparison with pharmacokinetic parameters in healthy subjects} \]

\[ \text{Median (range)} \]

Rifaximin is also an inhibitor of OATP, breast cancer resistance protein (BCRP) and a weak inhibitor of CYP3A4. The relative contribution of inhibition of each transporter by rifaximin to the increase in rifaximin exposure is unknown.

Effect of rifaximin on other drugs

In vitro drug interaction studies the IC50 values for rifaximin was >50 micromolar (~60 mcg) for CYP isozymes 1A2, 2C8, 2B6, 2C9, 2C19, 2D6, and 2E1. In vitro IC50 value of rifaximin for CYP3A4 was 25 micromolar. Based on in vitro studies, clinically significant drug interaction via inhibition of CYP3A4 is not expected.

The inhibitory effect of rifaximin on P-glycoprotein transport was observed in an in vivo study. The effect of rifaximin on P-gp transporter was not evaluated in vivo.

In vivo studies, rifaximin at 3 micromolar inhibited the uptake of estradiol glucuronide via OATP1B1 by 64% and via OATP1B3 by 70% while the uptake of estrone sulfate via OATP1A2 was inhibited by 40%. The inhibitory potential of rifaximin on these transporters at the clinically relevant concentrations is unknown.

Midazolam

In an in vivo 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-hydroxymidazolam, 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 Cmax of midazolam was 3.8% and 8.6%, respectively, than 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.

**Oral Contraceptives Containing Ethinyl Estradiol and Norgestimate**

The oral contraceptive study utilized an open-label, crossover design 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 0.025 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. 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.

#### 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 section: *Escherichia coli* (enterotoxigenic and enteraggregative strains).

#### Susceptibility Tests

*Vitro* susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI). However, the comparison 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 and female 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.rafsh2 mice dosed orally with rifaximin for 26 weeks at 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, or the 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, Peru, and India (Study 2). Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of XIFAXAN was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (Tlus) which was defined as the time to the last unformed stool passed, and adverse event 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 compared to placebo group. More patients treated with XIFAXAN were classified as clinical cure than those in the placebo group.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Tlus (hours)</th>
<th>N (%)</th>
<th>Clinical cure, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XIFAXAN (n=125)</td>
<td>32.5</td>
<td>58.6</td>
<td>2 (1.26, 2.50)</td>
</tr>
<tr>
<td>Placebo (n=129)</td>
<td>50 (78)</td>
<td>19 (19)</td>
<td></td>
</tr>
</tbody>
</table>

* Hazard Ratio (p-value <0.001)

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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall</th>
<th>Placebo</th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>38/53 (72)</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 diabetic 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 rates for these patients were 50% (9/18). 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 designed to evaluate 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.

#### 14.2 Hepatic Encephalopathy

The efficacy of XIFAXAN 550 mg taken orally two times per day for HE was evaluated in 3 randomized, multi-center, double-blind, placebo-controlled, parallel group Studies 1 and 2. Subjects were enrolled who had a MELD score of >25. The 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 with 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 and placebo groups respectively. 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. The oral contraceptive study utilized an open-label, randomized, placebo-controlled parallel group Study to establish in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients.

#### Figure 1: Kaplan-Meier Event-Free Curves in HE Study (Time to First Breakthrough HE 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=31), and those with 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 and placebo groups respectively. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE-related hospitalizations by 50% during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves is shown in Figure 2.

#### Figure 2: Kaplan-Meier Event-Free Curves in Pivotal HE Study (Time to First HE-Related Hospitalization in HE Study up to 6 Months of Treatment, Day 170) (ITT Population)

**Note:** Open diamonds and open triangles represent censored subjects.

* 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 with 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 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.
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 12 weeks/month in last 3 months associated with two or more of the following: 1. Improvement with defecation; 2. Onset associated with a change in form (appearance) of stool; 3. Onset associated with a change in 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.

### 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=315 (n (%))</th>
<th>Placebo n=320 (n (%))</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>144 (47) 116 (36)</td>
<td>8% (2.7%, 10.0%)</td>
<td></td>
</tr>
<tr>
<td>Stool Consistency Responders</td>
<td>233 (74) 206 (64)</td>
<td>10% (2.3%, 16.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Confidence Interval*  
The p-value for the composite endpoint for Trial 1 and 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 ≥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 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>Endpoint</th>
<th>XIFAXAN n=339 (n (%))</th>
<th>Placebo n=340 (n (%))</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain and Stool Consistency Responders</td>
<td>159 (51) 132 (42)</td>
<td>9% (1.9%, 17.0%)</td>
<td></td>
</tr>
<tr>
<td>Stool Consistency Responders</td>
<td>244 (79) 212 (68)</td>
<td>11% (4.4%, 18.2%)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>XIFAXAN n=312 (n (%))</th>
<th>Placebo n=320 (n (%))</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Relief of IBS Symptoms</td>
<td>126 (41) 98 (31)</td>
<td>10% (2.1%, 17.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Confidence Interval*  
The p-value for the primary endpoint for Trial 1 and for Trial 2 was <0.05.
15 REFERENCEs

16 HOW SUPPLIED/STORAGE AND HANDLING
The 200 mg tablet is a pink-colored, round, biconvex tablet with “Sx” debossed on one side. It is available in the following presentations:
• NDC 65649-301-03, bottles of 30 tablets

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

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

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 (5.4)].

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

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

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

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Salix Pharmaceuticals
Bridgewater, NJ 08807 USA

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Rifaximin for Travelers’ Diarrhea, Hepatic encephalopathy and IBS are protected by US Patent Nos. 7,045,620; 7,612,199; 7,902,206; 7,906,542; 8,158,781; 8,158,644; 8,193,196; 8,518,949; 8,741,904; 8,835,452; and 8,853,231. Rifaximin for Travelers’ Diarrhea is also protected by US Patent No. 7,928,115. Rifaximin for Hepatic encephalopathy is also protected by US Patent No. 8,642,573; 8,829,017; 8,946,252; and 8,969,398. Rifaximin for IBS is also protected by US Patent Nos. 6,681,053; 7,422,897; 7,716,608; and 8,309,569.

Web site: www.Salix.com