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Product Theater Reporter

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

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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 mortality[1];
- high rates of hospitalizations and associated costs[5,6];
- 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.

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intervening with recommended first-line therapy as quickly as possible,[8] along with secondary prophylaxis to reduce the risk of recurrent HE.[9]

Guidelines recommend using rifaximin (Xifaxan) for secondary prophylaxis after a patient has suffered an overt HE recurrence while on lactulose alone.[8] 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**).[10]

TABLE 1. Stages of HE[8]

Covert HE		Overt HE		
Minimal	I	II	III	IV
No observable symptoms Detectable only by psychometric testing	Euphoria or anxiety Trivial lack of awareness Shortened attention span Impaired ability to add or subtract Altered sleep rhythm	Lethargy or apathy Disorientation with respect to time Obvious personality change Inappropriate behavior Asterixis	Somnolence to semi-stupor Confusion Responsiveness to stimuli Gross disorientation Bizarre behavior	Coma

Abbreviation: HE, hepatic encephalopathy.

Overview of Hepatic Encephalopathy

Hepatic encephalopathy is a cerebral abnormality caused by liver insufficiency and/or portosystemic shunting.[8,11] It is characterized by an array of neuropsychiatric impairment and neuromuscular irregularities that lead to significant morbidity and mortality, and has a substantial impact on health care resource use.[1,12] Most patients with liver disease are likely to develop HE to some extent.[1] Moreover, it is one of the chief complications of end-stage liver disease, and thus a major issue for patients with cirrhosis.[1] The neurological and psychiatric abnormalities that manifest as a result of HE can range from subclinical alterations to coma.[8]

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.[13] Investigators recorded the presence and grade of HE at admission as well as the maximum grade during hospitalization.[13] 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;[13]
- 9% of the study population had the most severe HE, and they accounted for the majority of the deaths;[13]
- most of these patients had severe HE at admission.[13]

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.[13]

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**).[8] Minimal disease requires specialized psycho-

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metric testing to identify slight changes in neuropsychological function.[8] From there HE progresses to Grade I, where patients show mild neurologic changes, including euphoria or anxiety, as well as difficulty adding and subtracting.[8] Sleep and attention issues are also seen.[8]

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.[8] 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.[8]

Incidence and Prevalence

The majority of patients with liver disease will develop some form of HE.[1] Overt disease occurs in up to 45% of people with cirrhosis during their disease course,[1] and patients who reach this stage are very likely to experience recurring episodes.[5] 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.[8]

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.[1,5] A cross-sectional study involving 104 individuals with cirrhosis showed the financial burden of the condition to be substantial.[14] Sixty-three percent of patients felt that their financial status had decreased after diagnosis, and 44% stopped working.[14]

HE is a common cause of hospitalizations in patients with cirrhosis, and is likely to be under-recognized in both inpatient and outpatient settings.[5] 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).[15]

HE accounts for nearly 23,000 hospitalizations with an average stay of 8.5 days and average cost of more than $64,000.[15]

Patients with overt HE experience negative clinical outcomes, reduced quality of life, and social and occupational limitations, including permanent disability and difficulty driving.[11] 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).[15] 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.[15] Cognitive deficits and prolonged reaction times were primarily to blame.[15] Additionally, those with minimal HE had issues tied to attention deficits.[6]

Overt HE's impact extends beyond patients to their families and caregivers, who face financial stress, time burdens, health consequences, and mood problems.[14] Mild to severe depression and anxiety are seen in people who care for patients with overt HE.[14]

Overt HE also places considerable stress on the health care system, costing the United States approximately $7.2 billion each year.[6]

HE and Readmissions

Readmission rates for HE are high, and in fact are the highest among any complications of cirrhosis.[16] 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.[17] So even though HE itself is not currently identified as a core condition, patients with the disorder usually present with a core measure comorbidity.[18] 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.[18]

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.[7]

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).[16]

Early Identification and Management

Early diagnosis and treatment of HE is important to support good clinical and economic outcomes.[9] All patients with chirrhosis should be routinely assessed for HE symptoms, as this will help identify and manage HE more quickly.[9] If overt HE is observed, the patient should be referred to a liver unit immediately for prompt treatment initiation.[9] 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:[8]

- 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.[8] Additionally, lactulose overuse can lead to complications, such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation.[8]

Lactulose overuse might even encourage HE.[8] 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.[19]

Therefore, secondary prophylaxis is critical to reduce the risk of recurrence in patients recovering from their initial episode.[9] 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.[9]

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.[9] 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.[10]

Rifaximin for HE Management

Rifaximin is indicated for reduction in risk of overt HE recurrence in adults.[20] The recommended dose for overt HE is one 550 mg tablet taken orally twice a day.[20]

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.

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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.[20] The systemic exposure of rifaximin was elevated in patients with more severe hepatic impairment compared with healthy subjects.[20]

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.[10] 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.[10] 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 perotinitis, intercurrent infection, GI hemorrhage, transjugular intrahepatic portosystemic shunt (TIPS) placement within 3 months of screening, chronic renal or respiratory insufficiency, anemia, or electrolyte abnormality.[10]

The trial included 299 participants from 70 sites in 3 countries, including the United States (n=205), Canada (n=14), and Russia (n=80).[10] 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.[20] 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).[20] 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.[20] The range for MELD scores is 6 to 40, with higher numbers indicating more severe disease.[10] Nine percent of patients were Child-Pugh Class C.[20]

Participants were randomized 1:1 to receive rifaximin 550 mg twice daily (n=140) or placebo (n=159) for 6 months (**Figure 1**).[10] Lactulose was allowed throughout the trial, and 91% of patients in each treatment group received concomitant lactulose therapy.[10] 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.[10] 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.[10]

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.[20]

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.[10]

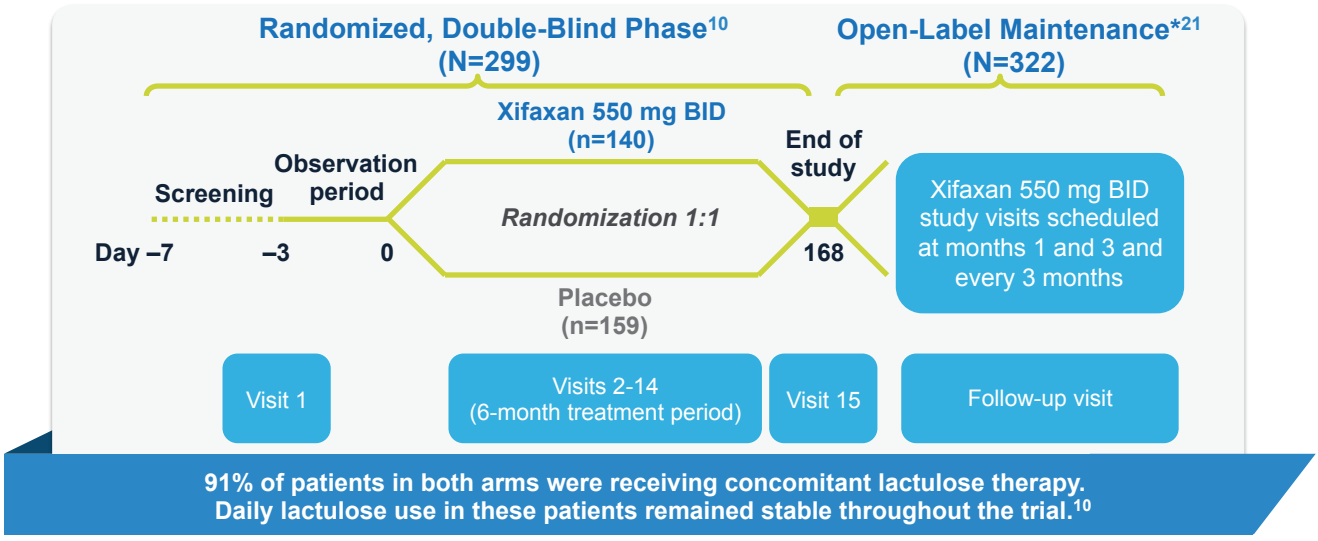
Reduced Risk of Breakthrough Overt HE as Well as Fewer HE-Related Hospitalizations

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**).[10] Breakthrough episodes of HE occurred in 22% of patients (31/140) who

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

- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

FIGURE 1. Study Design



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]

*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.[21]

Abbreviation: BID, twice a day.

received the study drug and 46% of patients (73/159) who received placebo at 6 months.[10] 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.[20]

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**).[10] 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.[10] HE-related hospitalizations were defined as hospitalizations directly resulting from HE, or hospitalizations complicated by HE.[20]

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.[10] The following adverse events occurred in ≥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%).

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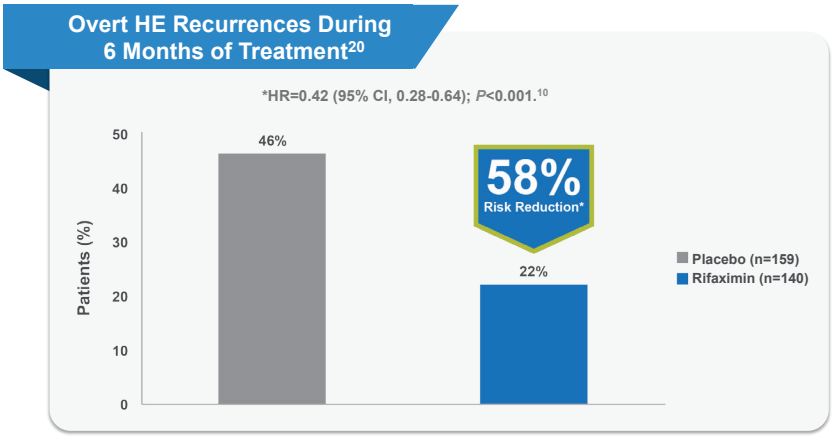
FIGURE 2. Rifaximin 550 mg Twice Daily Significantly Reduced the Risk of Overt HE Recurrence in Adults



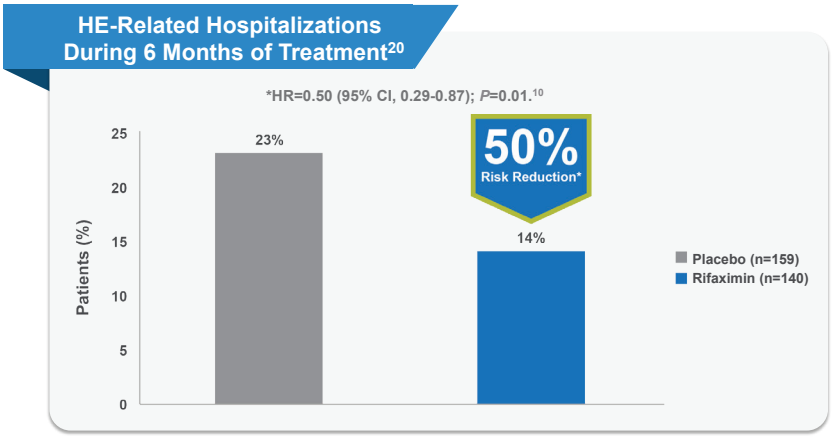
Breakthrough overt HE episode was defined as a marked deterioration in neurologic function and an increase in Conn score to Grade ≥2.

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.

FIGURE 3. Rifaximin 550 mg Twice Daily Significantly Reduced the Risk of HE-Related Hospitalizations in Adults



HE-related hospitalization was defined as hospitalization directly resulting from HE, or hospitalizations complicated by HE.

91% of patients across both arms of the trial concomitantly used lactulose.

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

of patients receiving rifaximin and at a higher rate than placebo: peripheral edema (15% vs 8%), nausea (14% vs 13%), dizziness (13% vs 8%), fatigue (12% vs 11%), and ascites (11% vs 9%).[10]

All-cause mortality was comparable between groups. Overall, 20 patients died during the study (9 in the rifaximin group and 11 in the placebo group). Most deaths were attributed to disease progression (eg, hepatic cirrhosis, decompensated cirrhosis, hepatic failure, alcoholic cirrhosis, end-stage liver failure).[10]

Number Needed to Treat

The numbers need to treat (NNT) using rifaximin to reduce the risk of 1 overt HE episode and 1 HE-related hospitalization are low compared with other medications and conditions (**Table 3**). For example:

- 140 patients would need to be treated with beta-blockers for 5 years,[22] and 12-26 patients treated with a statin for 10 years,[25] to prevent 1 cardiovascular event.
- 29 patients would need to be treated for 10 years with sulfonylurea-insulin, and 14 would need to be treated with metformin, to prevent 1 diabetes-related death.[23]
- 21 kidney transplant patients would need to be treated for 2 years with sirolimus or everolimus to prevent 1 case cytomegalovirus, and 18 to 41 patients would need the same 2-year treatment to prevent acute organ rejection.[24]

While this data cannot be compared across studies, with rifaximin 550 mg twice daily, only 4 patients would need to be treated for 6 months to reduce the risk of 1 episode of overt HE.[10] Just 9 patients would need to be treated for 6 months to reduce the risk of 1 HE-related hospitalization.[10]

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.

TABLE 2. Adverse Events in ≥10% of Patients Receiving Rifaximin and at a Higher Rate Than Placebo[10,20]

Adverse Event, n (%)	Rifaximin 550 mg BID (n=140)	Placebo (n=159)
Any event	112 (80)	127 (80)
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)

91% of patients in each treatment group were also taking lactulose therapy.[20]

Abbreviation: BID, twice a day.

TABLE 3. Rifaximin 550 mg Twice Daily – Number Needed to Treat in Relation to Other Therapeutic Classes

Condition	Treatment	To Address	NNT
Hypertension[22]	Beta-blockers	Cardiovascular event in 5 years	140
Diabetes[23]	Sulfony-lurea-insulin	Diabetes-related death in 10 years	29
Kidney transplant[24]	Sirolimus or everolimus	Cytomegalovirus disease for 2 years Acute rejection for 2 years	21 18-41
Cardiovascular disease[25]	Statins	Cardiovascular event in 10 years	12-26

• 4 patients would need to take Xifaxan 550 mg twice daily for 6 months to reduce the risk of 1 episode of overt HE[10]

• 9 patients would need to be treated with Xifaxan 550 mg twice daily for 6 months to reduce the risk of 1 HE-related hospitalization[10]

The above data is not a comparison of number needed to treat (NNT) among different treatments but is intended to provide an overview of published data on NNT.

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 Pglycoprotein (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.
- 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%).

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.

Conclusion

Symptoms of overt HE are debilitating and decrease the ability for self-care, which can lead to poor nutrition,

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treatment nonadherence, severe symptoms, frequent hospitalizations, and decreased life quality.[10] Rifaximin was proven to significantly reduce the risk of overt HE recurrences and HE-related hospitalizations.[10]

References

1. Jawaro T, Yang A, Dixit D, Bridgeman MB. Management of hepatic encephalopathy: a primer. *Ann Pharmacother*. 2016;50(7):569-577.

2. Volk ML, Tocco RS, Bazick J, et al. Hospital re-admisa sions among patients with decompensated cirrhosis. *Am J Gastroenterol*. 2012;107(2):247-252.

3. James J, Liou IW. Comprehensive care of patients with chronic liver disease. *Med Clin N A*m. 2015;99(5):913-933.

4. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepato*l. 2016;64(3):717-735.

5. Desai AP, Reau N. The burden of rehospitalization for patients with liver cirrhosis. *Hosp Practic*e. 2016;44(1):60-69.

6. Stepanova M et al. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clin Gastroenterol Hepatol*. 2012;10(9):1034-1041.

7. Tapper EB, Halbert B, Mellinger J, et al. Rates of and reasons for hospital readmissions in patients with cirrhosis: A multistate population-based cohort study. *Clin Gastroenterol Hepato*l. 2016;14(8):1181-1188.

8. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715-735.

9. Shawcross DL, Dunkc AA, Jalanb R, et al. How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist. *Euro J Gastroenterol Hepato*l. 2016;28(2):146-152.

10. Bass NM, Mullen KD, Sayal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Me*d. 2010;362(12):1071-1081.

11. Mullen KD, Ferenci P, Bass NM, et al. An algorithm for the management of hepatic encephalopathy. *Semin Liver Dis*. 2007;27(suppl2):32-47.

12. Liu A, Perumpail RB, Kumari R, Younossi ZM, Wong RJ, Ahmed A. Advances in cirrhosis: optimizing the management of hepatic encephalopathy. *World J Hepatol*. 2015;7(29):2871-2879.

13. Bajaj JS, O'Leary JG, Tandon P, et l. Hepatic encephalopathy is associated with mortality in patients with cirrhosis independent of other extrahepatic organ failures. *Clin Gastroenterol Hepatol*. 2017;15(4):565-574.e4.

14. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol*. 2011;106(9):1646-1653.

15. Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. *Gut Liver*. 2016;10(4):509-519.

16. Bajaj JS, Rajender Reddy K, Tandon P, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. *Hepatology*. 2016;64(1):200-208.

17. Zuckerman RB, Sheingold SH, Orav J, Ruther J, Epstein AM. Readmissions, Observation, and the Hospital Readmissions Reduction Program. *N Engl J Med.* 2016;374(16):1543-1551

18. Data on File. Health Economics Characterization of the Disease States of Cirrhosis and Hepatic Encephalopathy. Salix Pharmaceuticals, 2014.

19. Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. *Aliment Pharmacol Ther*. 2010;31(9):1012-1017.

20. Xifaxan [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals.

21. Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin Is Safe and Well Tolerated for Long-term Maintenance of Remission From Overt Hepatic Encephalopathy. *Clin Gastroenterol Hepatol*. 2014;12:1390-1397.

22. Wiysonge CSU, Bradley HA, Mayosi BM, et al. Beta-blockers for hypertension (review). *Cochrane Database Syst Rev*. 2007;1:CD002003.

23. Devries JH. Intensified glucose lowering in type 2 diabetes: don't throw the baby out with the bathwater. *Diabetologia*. 2011;54(3):705-706.

24. Webster AC, Lee VWS, Chapman JR, Craig JC. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. *Cochrane Database Syst Rev*. 2006;2:CD004290.

25. Mcelduff P, Jaefarnezhad M, Durrington PN. American, British and European recommendations for statins in the primary prevention of cardiovascular disease applied to British men studied prospectively. *Heart*. 2006;92(9):1213-1218.

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Faculty Disclosure: Dr. Ford discloses that he is on the educational advisory board and speakers' bureau for Salix Pharmaceuticals.

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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.

---------- RECENT MAJOR CHANGES ----------
Indications and Usage, Irritable Bowel Syndrome with Diarrhea (1.3) 5/2015
Dosage and Administration, Irritable Bowel Syndrome with Diarrhea (2.3) 5/2015

----------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 two 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)

----------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 inhibitor: Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor is needed (5.5, 7.2)

----------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 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------USE IN SPECIFIC POPULATIONS ----------
Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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.
- 550 mg – an oval tablet debossed with "rfx" on one side.

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 inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution 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 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 ≥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 ≥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 ≥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 ≥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

	Number (%) of Patients	
MedDRA Preferred Term	**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 ≥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:

- 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:

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)]*.

General

Hypersensitivity reactions, including 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.

7 DRUG INTERACTIONS

7.1 Effects of XIFAXAN on Other Drugs

Substrates of Cytochrome P450 enzymes

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

An *in vitro* study has suggested that rifaximin induces CYP3A4 *[see Clinical Pharmacology (12.3)]*. However, in patients with normal liver function, XIFAXAN at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

7.2 Effects of Other Drugs on XIFAXAN

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

Cyclosporine

Co-administration of cyclosporine, with XIFAXAN resulted in 83-fold and 124-fold increases in rifaximin mean C_{max} and AUC_{∞} in healthy subjects. The clinical significance of this increase in systemic exposure is unknown *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on XIFAXAN use in pregnant women to inform any drug associated risks. Teratogenic effects were observed in animal reproduction studies following administration of rifaximin to pregnant rats and rabbits during organogenesis at doses approximately 0.9 to 5 times and 0.7 to 33 times, respectively of the recommended human doses of 600 mg to 1650 mg per day. In rabbits, ocular, oral and maxillofacial, cardiac, and lumbar spine malformations were observed. Ocular malformations were observed in both rats and rabbits at doses that caused reduced maternal body weight gain *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the recommended dose for TD [600 mg per day], and approximately 1.3 to 2.6 times the recommended dose for HE [1100 mg per day], and approximately 0.9 to 1.8 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area). Rifaximin was teratogenic in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the recommended dose for TD [600 mg per day], and approximately 1.1 to 18 times the recommended dose for HE [1100 mg per day], and approximately 0.7 to 12 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area). These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar 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 per day (approximately 5 times the recommended dose for TD [600 mg per day], and approximately 2.6 times the recommended dose for HE [1100 mg per day], and approximately 1.8 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area).

8.2 Lactation

Risk Summary

There is no information regarding the presence of rifaximin in human milk, the effects of rifaximin on the breastfed infant, or the effects of rifaximin on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for XIFAXAN and any potential adverse effects on the breastfed infant from XIFAXAN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of XIFAXAN has not been established in pediatric patients less than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D.

8.5 Geriatric Use

Of the total number of patients in the clinical study of XIFAXAN for HE, 19% of patients were 65 and over, while 2% were 75 and over. In the clinical studies of IBS-D, 11% of patients were 65 and over, while 2% were 75 and over. No overall differences in safety or effectiveness were observed

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

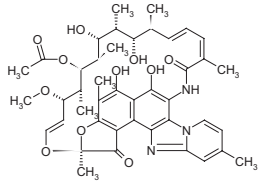
Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC_T) of rifaximin was about 10-, 14-, and 21-fold higher in those patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), 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.

11 DESCRIPTION

XIFAXAN tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-e] pyrido[1,2-á]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN tablets for oral administration are film-coated and contain 200 mg or 550 mg of rifaximin.

Inactive ingredients:

Each 200 mg tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifaximin is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Absorption

In healthy subjects, the mean time to reach peak rifaximin plasma concentrations was about an hour and the mean C_{max} ranged 2.4 to 4 ng/mL after a single dose and multiple doses of XIFAXAN 550 mg.

Travelers' Diarrhea

Systemic absorption of XIFAXAN (200 mg three times daily) was evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, $AUC_{0\text{-last}}$ estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 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_T) 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 T_{max} was 1 hour and mean C_{max} and AUC were generally comparable with those in healthy subjects. After multiple doses, AUC_{tau} was 1.65-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

	Healthy Subjects		IBS-D Patients	
	Single-Dose (Day 1) n=12	Multiple-Dose (Day 14) n=14	Single-Dose (Day 1) n=24	Multiple-Dose (Day 14) n=24
C_{max} (ng/mL)	4.04 (1.51)	2.39 (1.28)	3.49 (1.36)	4.22 (2.66)
T_{max} (h) [a]	0.75 (0.5-2.1)	1.00 (0.5-2.0)	0.78 (0-2)	1.00 (0.5-2)
AUC_{tau} (ng•h/mL)	10.4 (3.47)	9.30 (2.7)	9.69 (4.16)	16.0 (9.59)
Half-life (h)	1.83 (1.38)	5.63 (5.27)	3.14 (1.71)	6.08 (1.68)

[a] 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 C_{max}.

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 ^{14}C-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.

Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa.

Specific Populations

Hepatic Impairment

The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects.

The pharmacokinetics of rifaximin in patients with a history of HE was evaluated after administration of XIFAXAN 550 mg twice a day. The pharmacokinetic parameters were associated with a high variability and mean rifaximin exposure (AUC_T) in patients with a history of HE was higher compared to those in healthy subjects. The mean AUC_T 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).

Table 3. Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class[1]

	Healthy Subjects (n=14)	Child-Pugh Class		
		A (n=18)	B (n=15)	C (n=6)
AUC_{tau} (ng•h/mL)	12.3 ± 4.8	118 ± 67.8	169 ± 55.7	257 ± 100.2
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.4 ± 11.9	39.7 ± 13.4
T_{max} [2] (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (1.0, 4.2)	1 (0, 2)

[1] Cross-study comparison with pharmacokinetic parameters in healthy subjects

[2] Median (range)

Renal Impairment

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

Drug Interaction Studies

Effect of other drugs on rifaximin

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

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

Cyclosporine

In vitro in the presence of P-glycoprotein inhibitor, verapamil, the efflux ratio of rifaximin was reduced greater than 50%. In a clinical drug interaction study, mean C_{max} for rifaximin was increased 83-fold, from 0.48 to 40.0 ng/mL; mean AUC_∞ was increased 124-fold, from 2.54 to 314 ng•h/mL following co-administration of a single dose of XIFAXAN 550 mg with a single 600 mg dose of cyclosporine, an inhibitor of P-glycoprotein *[see Drug Interactions (7.2)]*.

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

Effect of rifaximin on other drugs

In *in vitro* drug interaction studies the IC_{50} values for rifaximin was >50 micromolar (~60 mcg) for CYP isoforms 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 2E1. *In vitro* IC_{50} value of rifaximin for CYP3A4 was 25 micromolar. Based on *in vitro* studies, clinically significant drug interaction via inhibition of 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4 by rifaximin is not expected.

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

In *in vitro* 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 vitro* 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 AUC of midazolam was 3.8% and 8.8% lower, respectively, than when midazolam was administered alone. The mean C_{max} 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 in 28 healthy female subjects to determine if XIFAXAN 200 mg orally administered three times a day for 3 days (the dosing regimen for travelers' diarrhea) altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.5 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by XIFAXAN.

An open-label oral contraceptive study was conducted in 39 healthy female subjects to determine if XIFAXAN 550 mg orally administered three times a day for 7 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.025 mg of ethinyl estradiol (EE) and 0.25 mg norgestimate (NGM). Mean C_{max} 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 C_{max} and AUC reductions in the presence of rifaximin is not known.

12.4 Microbiology

Mechanism of Action

Rifaximin is a semi-synthetic derivative of rifampin and acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase blocking one of the steps in transcription. This results in inhibition of bacterial protein synthesis and consequently inhibits the growth of bacteria.

Drug Resistance and Cross-Resistance

Resistance to rifaximin is caused primarily by mutations in the *rpoB* gene. This changes the binding site on DNA dependent RNA polymerase and decreases rifaximin binding affinity, thereby reducing efficacy. Cross-resistance between rifaximin and other classes of antimicrobials has not been observed.

Antibacterial Activity

Rifaximin has been shown to be active against the following pathogens both *in vitro* and in clinical studies of infectious diarrhea as described in the *Indications and Usage (1.1)* section:

Escherichia coli (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI).[1,2,3] However, the correlation between susceptibility testing and clinical outcome has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Malignant schwannomas in the heart were significantly increased in male Crl:CD® (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg per day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for TD, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for HE, based on relative body 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 efficacy 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)

	XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5% CI)
Median TLUS (hours)	32.5	58.6	2[a] (1.26, 2.50)
Clinical cure, n (%)	99 (79)	78 (60)	19[b] (5.3, 32.1)

[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 stool after 72 hours of therapy) rates for Study 1 are presented in Table 5 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though XIFAXAN had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

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

	XIFAXAN	Placebo
Overall	48/70 (69)	41/61 (67)
E. coli	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* in the stool (1); five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

14.2 Hepatic Encephalopathy

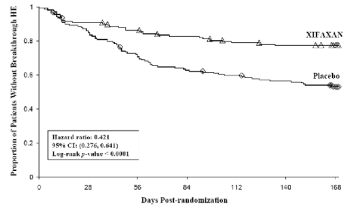
The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible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

A total of 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 ≤10 (27%) or 11 to 18 (64%) at baseline. No patients were enrolled with a MELD score of >25. Nine percent of the patients were Child-Pugh Class C. Lactulose was concomitantly used by 91% of the patients in each treatment arm of the study. Per the study protocol, patients were withdrawn from the study after experiencing a breakthrough HE episode. Other reasons for early study discontinuation included: adverse reactions (XIFAXAN 6%; placebo 4%), patient request to withdraw (XIFAXAN 4%; placebo 6%) and other (XIFAXAN 7%; placebo 5%).

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

Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in the XIFAXAN group and by 73 of 159 subjects (46%) in the placebo group during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE breakthrough by 58% during the 6-month treatment period. Presented below in Figure 1 is the Kaplan-Meier event-free curve for all subjects (n=299) in the study.

Figure 1: Kaplan-Meier Event-Free Curves[1] in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)

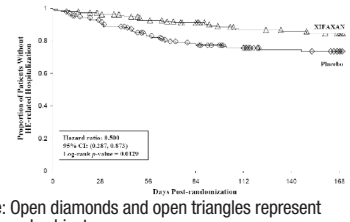


Note: Open diamonds and open triangles represent censored subjects.
[1] Event-free refers to non-occurrence of breakthrough HE.

When the results were evaluated by the following demographic and baseline characteristics, the treatment effect of XIFAXAN 550 mg in reducing the risk of breakthrough overt HE recurrence was consistent for: sex, baseline Conn score, duration of current remission and diabetes. The differences in treatment effect could 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 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[1] 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

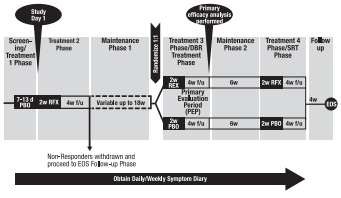
three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period. The Rome II criteria further categorizes IBS patients into 3 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or alternating IBS (bowel habits alternating between 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 (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 2579 were enrolled to receive open-label XIFAXAN for 14 days. Of 2438 evaluable patients, 1074 (44%) responded to initial treatment and were evaluated over 22 weeks for continued response or recurrence of IBS-symptoms. A total of 636 patients had symptom recurrence and were randomized into the double-blind 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 ≥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 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 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

	Trial 1		
Endpoint	**XIFAXAN n=309 n (%)**	**Placebo n=314 n (%)**	**Treatment Difference (95% CI[a])**
Adequate Relief of IBS Symptoms[b]	126 (41)	98 (31)	10% (2.1%, 17.1%)
	Trial 2		
Endpoint	**XIFAXAN n=315 n (%)**	**Placebo n=320 n (%)**	**Treatment Difference (95% CI[a])**
Adequate Relief of IBS Symptoms[b]	128 (41)	103 (32)	8% (1.0%, 15.9%)

[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

	Trial 1		
Endpoint	**XIFAXAN n=309 n (%)**	**Placebo n=314 n (%)**	**Treatment Difference (95% CI[a])**
Abdominal Pain and Stool Consistency Responders[b]	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%)
	Trial 2		
Endpoint	**XIFAXAN n=315 n (%)**	**Placebo n=320 n (%)**	**Treatment Difference (95% CI[a])**
Abdominal Pain and Stool Consistency Responders[b]	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%)

[a] Confidence Interval
[b] 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, 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 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 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[a])**
Combined Responder[c]: Abdominal Pain and Stool Consistency Responders[c]	97 (31)	125 (38)	7% (0.9%, 16.9%)
Abdominal Pain Responders *(≥30% reduction in abdominal pain)*	130 (42)	166 (51)	9% (1.6%, 17.0%)
Stool Consistency Responders *(≥50% reduction from baseline in days/week with loose or watery stools)*	154 (50)	170 (52)	2% (-4.7%, 11.0%)

[a] Confidence Intervals were derived based on CMH test adjusting for center and patients' time to recurrence during maintenance phase.
[b] Primary endpoint
[c] 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%).

15 REFERENCES

1. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard Ninth Edition. CLSI document M07-A9. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.
2. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard Eighth Edition. CLSI document M11-A8. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.
3. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. CLSI document M100-S2. Wayne, PA: Clinical and Laboratory Standards Institute, 2014.

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Rev. 11/2015

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 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. 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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