

Drug Evaluation: rifaximin tablets, oral

Month/Year of Review: May 2015

Generic Name: rifaximin

End Date of Literature Search: February 2015

Brand Name (Manufacturer): Xifaxan® (Salix Pharmaceuticals)

Research Questions:

- Is rifaximin more effective than currently available alternative agents for the prevention or treatment of hepatic encephalopathy (HE)?
- Is rifaximin safer than currently available agents used to prevent or treat HE?
- Are there subgroups of patients in which rifaximin may be safer or more effective than other drugs to prevent or treat HE?

Conclusions and Recommendations:

- There is insufficient evidence that rifaximin is superior to lactulose for preventing episodes of overt HE. However, there is low quality evidence that adding rifaximin 550 mg twice daily to an adequate lactulose regimen for 6 months is statistically superior to lactulose alone at preventing episodes of HE by 24% (Hazard ratio [HR] 0.42 (95% CI, 0.28 to 0.64; $p < 0.001$; number needed to treat [NNT] 4)¹ and improving quality-of-life, as shown by a difference of about 0.5 to 1 point on all 6 domains of the 7-point Chronic Liver Disease Questionnaire, in patients with a frequent history of hepatic encephalopathy.²
- There is low quality evidence that adding rifaximin at a daily dose of 1200 mg to an adequate lactulose regimen in hospitalized patients with overt HE is statistically superior to lactulose alone at treating overt HE within 10 days (76% vs. 44%, respectively; $p = 0.004$), decreasing hospital stay (5.8 ± 3.4 vs. 8.2 ± 4.6 days, respectively; $p = 0.001$), and improving 10-day mortality (24% vs. 49%, respectively; $p < 0.05$).³ Studies have not been conducted in the U.S. for this off-label use. Despite lack of evidence, both agents are increasingly used concomitantly to treat overt hepatic encephalopathy.
- There is low quality evidence that rifaximin is equivalent to lactulose for the treatment of overt encephalopathy.⁴⁻⁶ Larger trials need to be conducted to adequately differentiate between these two treatments for this off-label use.
- There is insufficient evidence for the use of rifaximin without lactulose to prevent or treat hepatic encephalopathy.
- There is moderate quality evidence that rifaximin is associated with less diarrhea than lactulose.⁴ Overall, rifaximin is well tolerated with no attributable serious adverse effects.^{1,7} Cases of *Clostridium difficile* infection were observed in rifaximin-treated patients and it remains to be seen how long-term therapy may affect rates of infection in this already high-risk population.⁷
- There is insufficient evidence that any subgroups may benefit from rifaximin more than the general population for which it has been studied. Etiology of cirrhosis (alcohol, hepatitis C, fatty liver, etc.) does not appear to affect efficacy or safety. All patients studied were adults, most being white males under the age of 65 years.
- Establish Prior Authorization (PA) criteria so use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. Require concomitant use of adequately dosed lactulose when used to prevent or treat HE and discourage use of drugs known to precipitate hepatic encephalopathy (e.g., benzodiazepines). See Appendix 2 for the recommended PA criteria.

Background:

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric complication of cirrhosis with wide variety of clinical manifestations.⁸ The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency. Patients with cirrhosis are most affected with an incidence of HE between 5-25% within 5 years of diagnosis, depending on other risk factors present.⁹ Overt HE will occur in 30-40% of those with cirrhosis at some time during their clinical course, and will occur repeatedly in the survivors in most cases.⁹ The prevalence of HE continues to rise primarily because patients with chronic hepatitis C, typically born between 1945 and 1965, are now developing cirrhosis and the obesity epidemic, which fuels nonalcoholic fatty liver disease and its complications, are developing at a more rapid pace.¹⁰ More than 110,000 patients are admitted for overt HE every year to hospitals in the U.S.⁹

Hepatic encephalopathy can be classified in stages – often called West Haven criteria, or Conn scores⁸:

- Stage 0 = no detectable changes in personality or behavior, no asterixis;
- Stage 1 = trivial lack of awareness, shortened attention span, dyscalculia, euphoria, depression, anxiety, hypersomnia or insomnia, asterixis may be seen;
- Stage 2 = lethargy, apathy, disorientation, inappropriate behavior, slurred speech, subtle personality change, obvious asterixis;
- Stage 3 = gross disorientation, confusion, bizarre behavior, asterixis usually absent, somnolence or stupor;
- Stage 4 = coma

Asterixis or “flapping tremor” is often present in the early to middle stages of HE that precede stupor or coma. It is not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers.⁹ Asterixis is graded as follows¹:

- 0 = no tremors;
- 1 = few flapping motions;
- 2 = occasional flapping motions;
- 3 = frequent flapping motions;
- 4 = almost continuous flapping motions

The West Haven criteria are the gold standard for the diagnosis of overt HE. However, it is subjective with limited inter-observer reliability, especially for Stage 1 because signs are often overlooked in clinical examination.⁹ In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of overt HE.⁹

The exact pathogenesis of HE is unknown but the common theory is nitrogenous compounds (i.e., ammonia) produced by colonic bacteria in the gastrointestinal tract build up in systemic circulation due to decreased hepatic function.⁸ The nitrogenous substances cross the blood-brain barrier and enter brain tissue, causing extensive degeneration and increased rates of cellular apoptosis.⁸ This neurotoxic effect on brain tissue results in cerebral edema, inflammation, and altered neurotransmission affecting consciousness and behavior.⁸ However, although cirrhotic patients with HE often have elevated ammonia levels, there is no absolute correlation between ammonia and grade of HE.¹⁰ Indeed, other proposed mechanisms of pathogenesis include inflammatory cytokines and benzodiazepine-like compounds, such as gamma-aminobutyric acid, which have been reported to play a role.¹⁰ In addition, up to 80% of episodes of HE are precipitated by an event such as an infection, electrolyte abnormality or gastrointestinal bleeding.¹¹

Treatment for HE aimed at managing the precipitating factors (i.e., electrolyte abnormality, constipation, infection, etc.) and reducing ammonia levels has resulted in clinical improvement.¹⁰ At this time, only overt HE is routinely treated – during the acute episode and as secondary prophylaxis.⁹ The non-absorbable disaccharide lactulose and the antibiotic rifaximin are the mainstay of pharmacological management. Lactulose reduces ammonia levels by its laxative effect combined with its acidification of the colon with resultant conversion of ammonia to ammonium, which shifts the colonic flora to non-urease-producing bacteria. Results from placebo-controlled studies of lactulose are limited by significant heterogeneity of types of HE (minimal vs. overt), differences in prognostic importance of precipitants and subjectivity of assessment tools.¹¹ Still, decades of clinical experience with lactulose speaks to its effectiveness for secondary prevention of HE and to its ability to effectively reverse episodic, overt HE.¹¹ Indeed, the current guideline by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommends lactulose as initial treatment for episodic, overt HE.⁹ Rifaximin is a minimally absorbed oral antibiotic that is concentrated in the gastrointestinal tract and has broad-spectrum *in vitro* antimicrobial activity. Rifaximin has been primarily studied for secondary prevention of episodic, overt HE in patients in remission at time of enrollment.¹ Rifaximin is well-tolerated but no solid data support the use of rifaximin alone and it remains very costly.^{9,11} As such, AASLD/EASL recommends rifaximin as an effective add-on therapy to lactulose for secondary prevention of overt HE.⁹ The addition of rifaximin to lactulose for episodes of overt HE is an increasingly common practice.¹¹ Many other drugs (i.e., oral branched-chain amino acids, intravenous L-ornithine L-aspartate, neomycin, metronidazole, etc.) have been used for treatment of overt HE, but data to support their use are limited or lacking altogether.

Rifaximin received an FDA-approved indication in 2010 for reduction in risk of overt HE recurrence in adults. Rifaximin also has an FDA-approved indication for treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli*.¹² Both HE and infectious diarrhea are funded conditions under the OHP. See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Other uses of rifaximin with insufficient evidence includes relief of bloating and flatulence common in irritable bowel syndrome (IBS) and treatment for rosacea, purported to be induced by intestinal bacterial overgrowth.¹³ Both IBS and rosacea are non-funded conditions under the OHP. Increasing use and substantial cost associated with this drug necessitates a formal review of its evidence for OHP-funded conditions.

Clinical Efficacy:

Data from one randomized controlled trial (RCT) by Bass, et al.¹ which compared rifaximin (n = 140) to placebo (n = 159) for the prevention of HE was evaluated by the FDA for approval.^{1,14} In this study, more than 90% of patients in each group also received lactulose therapy. Mean age of the patients was 56 years, 86% of which were whites and 61% males. Most patients had a Conn score of 0 (67%) and 0 grade asterixis (68%) at baseline. Most patients (64%) had a Model for End-Stage Liver Disease (MELD) score of 11-18 (MELD range 6 to 40, with higher scores indicating more severe liver disease). Rifaximin or placebo was continued for 6 months or until an episode of HE occurred, whichever came earlier. The primary outcome studied was time to first episode of HE, defined as time to increase Conn score of 0 or 1 at baseline to 2 or greater; or time to increase Conn score of 0 at baseline to 1 plus an 1-grade increase in asterixis. The study did not report time to first episode of HE. Rather, it was reported that compared to placebo, patients in the rifaximin group had significantly greater reductions in first breakthrough HE episode (22.1% vs. 45.9%) during the study period. The associated HR was 0.42 (95% CI, 0.28 to 0.64; p<0.001; NNT 4). A secondary outcome was time to first hospitalization involving HE. Again, the study did not report time to first HE-related hospitalization. Rather, the proportion of patients with an HE-related hospitalization was reported, which favored rifaximin compared to placebo (13.6% vs 22.6%). The associated HR was 0.50 (95% CI, 0.29 to 0.87; p=0.01). Unfortunately, method of randomization, and thus concealment of allocation, are uncertain. A double-dummy design was not described so blinding may not have been maintained. Overall attrition rate was high with a substantial difference between the two groups. Another concern for bias is the use of Conn score because it is not known to be sensitive in differentiating milder severities of HE and is dependent on clinical judgement.¹⁴ Adverse drug events and

mortality were similar in both groups. The authors concluded that rifaximin in combination with lactulose was effective in preventing breakthrough HE in patients with recurrent HE and cirrhosis. Detailed data and analysis of this study is provided in the **Comparative Evidence Table**.

In a concurrent study, the original investigators also evaluated the effect of rifaximin (n=101) versus placebo (n=118) on health-related quality of life (HRQL) in 219 patients.² Most patients in both groups (94%) concurrently took lactulose. The relationship between HRQL and breakthrough HE episode was also assessed. HRQL was measured by the Chronic Liver Disease Questionnaire (CLDQ), the first validated, disease-specific HRQL instrument developed to measure longitudinal change over time in patients with chronic liver disease. The CLDQ includes 29 items in the following 6 domains: abdominal symptoms (3 items), fatigue (5 items), systemic symptoms (5 items), activity (3 items), emotional function (8 items) and worry (5 items). Patient-rated responses for each question were ranked on a 7-point scale, with higher scores indicating better HRQL. Data are presented by domain and overall. Inclusion and exclusion criteria were identical to the Bass, et al. study¹ and baseline characteristics were similar as well. The mean duration of treatment was about 4 months in the rifaximin group and 3 months in the placebo group. Results showed that patients who received rifaximin had significant improvement in CLDQ scores compared to the placebo group. Differences in CLDQ scores were only presented visually but there appeared to be an improvement of 0.5 to 1 point for each domain. There also appeared to be a direct correlation between a poorer CLDQ score and experiencing an overt HE during the study period. The Spearman correlation coefficient for overall CLDQ and breakthrough HE was 0.5830 (95% CI, -0.67 to -0.49). The authors concluded that HRQL significantly improved in patients who received rifaximin in combination with lactulose and that worsening HRQL may predict HE events, irrespective of treatment.²

Rifaximin use for episodic overt HE in hospitalized patients, in addition to lactulose, have become a common 'off-label' practice despite little evidence.¹¹ Older trials that evaluated rifaximin for episodic HE used different comparators and generally enrolled small numbers of patients with acute, chronic, or unclear acuity of HE.¹¹ More recently however, a single-centered RCT was conducted in India to compare rifaximin with lactulose (n=63) to lactulose and placebo (n=57) in patients with overt HE.³ Rifaximin was dosed at 1200 mg daily using 400 mg capsules which are not available in the U.S. Lactulose was appropriately dosed at 30-60 mL three times daily, titrated so that patients passed 2-3 semisoft stools per day. Treatment continued for a maximum of 10 days or until complete recovery of HE. Mean age was 39 years and 80% of patients had severe HE, grade III or IV, and 69% were Child Class C with primarily alcohol-related etiology. Patients in the lactulose and rifaximin group had a higher proportion of complete reversal of HE within 10 days (76% vs. 44%; p=0.004), shorter hospital stay (5.8±3.4 vs. 8.2±4.6 days; p=0.001), and a striking improvement in 10 day mortality (24% vs 49%; p<0.05).³ Unfortunately, the very high mortality in the lactulose plus placebo arm raises some concerns about the validity of this study, which should be repeated in a larger number of patients at multiple sites. Overall quality of evidence from this study is methodologically poor due to poor blinding methods and small study size. Applicability of the study may be limited due to its single-centered design.

In addition to the clinical trials presented here, three systematic reviews⁴⁻⁶ have been conducted looking at older studies evaluating rifaximin for the treatment of overt HE. The only exception is two trials identified in a recent systematic review⁶ that also included evaluation of the FDA-approved indication for prevention of HE. Trials eligible for these reviews were primarily conducted in Italy, followed by South Korea or Spain using a 1200 mg per day dose which is slightly higher than the 1100 mg per day dose approved in the U.S. Trials evaluated in these reviews were small, with the Bass, et al.¹ study evaluating rifaximin for prevention of HE and used for FDA approval in the U.S. being the largest trial (n=299), as much as 7- to 8-fold larger than most of the other eligible studies included (n=30 to 50).

The most recent systematic review was performed to evaluate the effects of rifaximin for patients with HE.⁶ Eligible studies included RCTs of rifaximin for the prevention of HE or in patients with minimal or overt HE. Over half of the included trials were conducted in Italy. Most trials were of patients with cirrhosis largely related to alcohol or viral hepatitis. Doses ranged from 1100 to 1200 mg per day and treatment lasted between 5 and 180 days. The study oddly included

control patients that received either a placebo, a non-absorbable oral disaccharide (i.e., lactulose) or another antibiotic. The primary outcomes were prevention, recovery and improved manifestation of HE. A statistically significant effect was found with rifaximin for the prevention of overt HE (Relative Risk [RR] 1.36; 95% CI, 1.06 to 1.65; n=2 RCTs) and for full resolution of overt HE (RR 1.34; 95% CI, 1.11 to 1.62; n=11 RCTs; $I^2=54\%$; Number Needed to Treat [NNT] 6) without evidence of publication bias. There were no significant differences between rifaximin and controls for serious adverse events (n=13 RCTs).⁶ Interpreting the results of this review is difficult considering the heterogeneity of the indications, populations and the combination of both placebo and active-control groups for treatment of overt HE.

The other two systematic reviews^{4,5} analyzed trials comparing rifaximin against active controls for treatment of overt HE:

A very well conducted systematic review was performed to compare rifaximin with conventional oral therapy for overt HE.⁵ Eligible studies included RCTs reporting on the effectiveness of rifaximin compared with non-absorbable oral disaccharides or other antibiotics in patients with overt HE. Primary outcomes included improvement in neurological function, the grade of HE according to Conn scores (see explanation in Evidence Table) and safety. All studies evaluated rifaximin 400 mg three times daily (1200 mg per day), which is slightly higher than the 1100 mg per day dose used in the U.S. Control arms primarily received lactulose 35-120 mL per day or neomycin 3000-4500 mg/day. Treatment duration ranged from 7 days to 6 months. Seven trials compared rifaximin with disaccharides (mostly lactulose) and reported that both groups experienced either full resolution of HE or a clinically significant improvement, but there was no statistically significant difference between the groups. A similar result was seen in the 5 trials comparing rifaximin with other antibiotics (mostly neomycin). The overall odds ratio (OR) for patients receiving disaccharides or antibiotics showed a trend that favored the use of rifaximin at improving neurological function in overt HE but the difference was not significantly different (OR 1.96; 95% CI, 0.94 to 4.08; $I^2=27\%$). Patients with rifaximin had lower rates of diarrhea (OR 0.20; 95% CI, 0.04 to 0.92; 8 RCTs; $I^2=66\%$) though rates of abdominal pain, nausea and weight loss were similar between the groups. The authors concluded rifaximin was similar to other oral therapies in its clinical efficacy for HE but has fewer adverse effects.⁵

When specifically comparing rifaximin to non-absorbable disaccharides, a separate systematic review evaluated RCTs treating overt HE.⁴ Eight RCTs were eligible for inclusion, all conducted in South Korea, Italy or Spain for a total duration ranging from 7 days to 3 months using a dose of 1200 mg per day of rifaximin and 45-120 mL per day of lactulose (or 60 g per day of lactitol). The meta-analysis showed no significant difference between rifaximin and non-absorbable disaccharides in their efficacy for treating HE, serum ammonia levels, mental status and asterixis (flapping tremor). However, rifaximin was associated with lower rates of diarrhea (RR 0.11; 95% CI, 0.04 to 0.31; $I^2=48\%$; 5 RCTs) and less abdominal pain (RR 0.34; 95% CI, 0.14 to 0.83; $I^2=33\%$; 6 RCTs). Unfortunately, only five of the included trials described their randomization process, six trials described allocation concealment, and only three trials blinded the observers. In addition, the authors found presence of publication bias. The small sample sizes, some statistical heterogeneity and limitations in the quality of the included trials make the reliability of these findings uncertain.⁴

Clinical Safety:

The original investigators of the Bass, et al.¹ study further evaluated the effect of long-term (median exposure about 14 months) rifaximin on safety and durability of treatment in a phase 3, open-label, non-controlled maintenance study.⁷ Inclusion and exclusion criteria were the similar to the original study. Most patients (mean age 57 years) concurrently took lactulose (90%) and had a MELD score of 11-18 (59%) with a Conn score of 0 (64%) and an asterixis grade of 0 (68%). Baseline characteristics were similar except that patients on rifaximin had a significantly longer duration of remission at time of enrollment compared to the historical control group from the original study. The results showed that rifaximin remained well-tolerated. Adverse event rates did not increase compared to the historical rates seen in the original 6-month study. Most adverse events observed were related to the underlying liver disease. A total of 76 patients (19%) died during the study of which most could be attributed to complications of cirrhosis, followed by cardiac causes and infection. Six cases of *Clostridium difficile*

infection were identified in patients treated with rifaximin versus none in the historical control group. None of the deaths were attributed to rifaximin treatment. Overall, morality and rate of hospitalizations for overt HE were similar to the historical control group in the original 6-month study.⁷

The adverse events associated with 6-month use of rifaximin compared to placebo are summarized in Table 1. There were no statistically significant differences between the two groups for these events and most observed events were related to the underlying chronic liver disease.¹ Note that 91% of patients in both groups concurrently received lactulose therapy.

Table 1. Adverse Events Associated with Rifaximin and Placebo.¹

Event	Rifaximin (n=140)	Placebo (n=159)	Event	Rifaximin (n=140)	Placebo (n=159)
Any Event	80.0%	79.9%	Vomiting	7.1%	8.8%
Nausea	14.3%	13.2%	Insomnia	7.1%	6.9%
Diarrhea	10.7%	13.2%	Depression	7.1%	5.0%
Fatigue	12.1%	11.3%	Cough	7.1%	6.9%
Peripheral Edema	15.0%	8.2%	Constipation	6.4%	6.3%
Ascites	11.4%	9.4%	Upper Abdominal Pain	6.4%	5.0%
Dizziness	12.9%	8.2%	Pyrexia	6.4%	3.1%
Headache	10.0%	10.7%	Back Pain	6.4%	6.3%
Muscle Spasms	9.3%	6.9%	Arthralgia	6.4%	2.5%
Pruritus	9.3%	6.9%	Dyspnea	6.4%	4.4%
Abdominal Pain	8.6%	8.2%	Urinary Tract Infection	5.7%	8.8%
Abdominal Distension	7.9%	7.5%	Rash	5.0%	3.8%
Anemia	7.9%	3.8%	Asthenia	2.9%	7.5%

Look-alike / Sound-alike Error Risk Potential: none

Pharmacology and Pharmacokinetic Properties¹²:

Parameter	
Mechanism of Action	Binds the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of RNA synthesis
Oral Bioavailability	Minimal systemic absorption
Distribution and Protein Binding	Moderately bound to human plasma protein (62% in patients with hepatic impairment)
Elimination	97% excreted unchanged in feces
Half-Life	Not applicable
Metabolism	Not applicable

		intrahepatic portosystemic shunt in last 3 months; ●Renal insufficiency (SCr >2.0 mg/dL) ●Respiratory insufficiency ●Anemia (Hgb <8.0 g/dL) ● Electrolyte abnormalities (Na+ <125 mEq/L or K+ <2.5 mEq/L or Ca+2 >10 mg/dL) ●Active infection ●Active SBP ●BZDs or BZD-like drugs ●Narcotics ●Psychotropic drugs		HR 0.50 (95% CI, 0.29 to 0.87; p=0.01)				<p>Outcomes: Conn Score is known not to be sensitive in differentiating milder severities of HE. It is somewhat imprecise (it can fluctuate throughout the day) and depends on clinical judgment.</p> <p>Setting: Not detailed but probably outpatient clinics. Not studied in hospitalized patients with OHE.</p> <p>Analysis:</p> <ul style="list-style-type: none"> ●Study designed and sponsored by Salix Pharmaceuticals; data collected under the supervision of Salix Pharmaceuticals; final manuscript edited by Salix Pharmaceuticals. ●Study stopped after first episode of HE. Mean duration (\pmSD) of treatment of rifaximin was 130.3\pm56.5 days and placebo was 105.7\pm62.7 days.
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Abbreviations [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; BID = twice daily; BZD = benzodiazepines; Ca+2 = serum calcium; CI = confidence interval; DB = double-blind; dL = deciliter; g = grams; HE = hepatic encephalopathy; Hgb = hemoglobin; ITT = intention to treat; K+ = serum potassium; L = liter; MC = multicenter; MELD = Model for End-Stage Liver Disease scale (score range 6 to 40, with higher scores indicated more severe disease); mEq = milliequivalents; mg = milligrams; mITT = modified intention-to-treat; N = number of subjects; Na+ = serum sodium; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OHE = overt hepatic encephalopathy; PO = by mouth; RCT = randomized controlled trial; SBP = spontaneous bacterial peritonitis; SCr = serum creatinine; SD = standard deviation; y = years.

***Conn Scores:**

- 0 = no personality or behavioral abnormality detected;
- 1 = trivial lack of awareness, euphoria or anxiety, shortened attention span, or impairment of ability to add or subtract;
- 2 = lethargy, disorientation with respect to time, obvious personality change, inappropriate behavior;
- 3 = somnolence or semi-stupor, responsiveness to stimuli, confusion, gross disorientation, or bizarre behavior; and
- 4 = coma

****Asterixis Grades:**

- 0 = no tremors;
- 1 = few flapping motions;
- 2 = occasional flapping motions;
- 3 = frequent flapping motions; and
- 4 = almost continuous flapping motions

References:

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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
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, Hepatic Encephalopathy (1.2) 03/2010
Dosage and Administration, Hepatic Encephalopathy (2.2) 03/2010

-----**INDICATIONS AND USAGE**-----

XIFAXAN is a rifamycin antibacterial indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* (1.1)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age (1.2)

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)

-----**DOSAGE AND ADMINISTRATION**-----

- Travelers' diarrhea: One 200 mg tablet taken orally three times a day for 3 days, with or without food (2.1)
- Hepatic encephalopathy: One 550 mg tablet taken orally two times a day, with or without food (2.2)

-----**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 (4.1)

-----**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 24-48 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 C) hepatic impairment (5.4, 8.7)
- Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor is needed (5.5,7.2).

-----**ADVERSE REACTIONS**-----

- Most common adverse reactions in travelers' diarrhea (≥ 5%): Flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea (6.1)
- Most common adverse reactions in HE (≥ 10%): Peripheral edema, nausea, dizziness, fatigue, and ascites (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: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2014

Rifaximin (Xifaxan®)

Goal:

- To optimize appropriate pharmacological management of prevention and treatment of hepatic encephalopathy.

Length of Authorization:

6 months to Lifetime

Requires PA:

- Rifaximin

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the treating diagnosis prevention or treatment of hepatic encephalopathy (572.2)?	Yes: Go to 4	No: Go to 3
3. Is the treating diagnosis treatment of traveler's diarrhea (009.2)?	Yes: Approve 3-day supply Note: FDA-labelled dosing is 200 mg three times daily for 3 days	No: Pass to RPH. Deny if treating condition is not funded by OHP. Approve for 6 months if condition is funded by OHP with adequate supporting literature.
4. Is the patient currently managed with an adequate daily dose of lactulose?	Yes: Go to 5	No: Go to 7
5. Is the patient currently prescribed a benzodiazepine drug?	Yes: Go to 6	No: Approve for lifetime
6. Will the prescriber consider safely tapering the patient off the benzodiazepine (tapering process may be several months)?	Yes: Approve for 1 year	No: Inform prescriber that studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy. If justification is given for not tapering off the benzodiazepine, approve for 6 months.

Approval Criteria

7. Does the patient have a contraindication to lactulose?	Yes: Approve for lifetime	No: Inform prescriber studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose. If justification is given for not treating with lactulose, approve for 6 months.
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P&T / DUR Action: 5/15 (AG)
Revision(s):
Initiated: **TBD**