SPECIAL REPORT

Reduction of Overt HE Recurrence Risk Using Rifaximin: Real-World Evidence and Perspectives

This resource was developed and sponsored by Salix Pharmaceuticals.

Faculty

Arun Jesudian, MD
Transplant Hepatologist
Associate Professor, Clinical Medicine
New York-Presbyterian Hospital/Weill Cornell
New York, NY

Corrie Berk, DNP, MBA
Transplant Hepatology Nurse Practitioner
Director, Hepatology & Transplant
Outreach Programs
Texas Liver Institute
Austin, TX

This Special Report features real clinicians who have been compensated by Salix Pharmaceuticals for their participation. The content is based on their own personal experiences.

Inside

Overt HE: Overview and Management With Rifaximin *2*

CLINICAL HIGHLIGHT #1:
Real-World Evidence of Rifaximin Efficacy After an HE-Related Hospitalization *4*

CLINICAL HIGHLIGHT #2:
Importance of Transition of Care in Patients With HE *6*

Key Highlights

- Overt hepatic encephalopathy (OHE) commonly occurs as a result of decompensated cirrhosis, which causes patients to have a decreased ability to break down toxins (eg, ammonia) that can impact the brain.[1,2]
- Patients experiencing OHE can show a range of neuropsychiatric symptoms, including personality changes, disorientation, somnolence, and cognitive deficits.[2]
  - Symptoms can be severe and recurring, causing frequent hospitalizations and readmissions.[2,3]
- XIFAXAN® (rifaximin) is an FDA-approved nonsystemic antibiotic for the reduction in risk of OHE recurrence in adults.[4]
  - There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering rifaximin to these patients.[4]
- A real-world healthcare claims analysis of patients hospitalized with OHE assessed the risk of OHE rehospitalization within 30 days of discharge and the annual rate of OHE rehospitalization.[5]
  - Patients prescribed rifaximin immediately upon discharge from an OHE hospitalization had the greatest reduction in risk of 30-day rehospitalization and annual rates of rehospitalization due to OHE compared to patients treated with rifaximin with delay, lactulose alone, or neither rifaximin nor lactulose.[5]

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.

Overt HE: Overview and Management With Rifaximin

Cirrhosis

Patients with chronic liver disease (CLD) can progressively accumulate diffuse liver damage over time and develop cirrhosis.[1] The prevalence and mortality of cirrhosis has been increasing over the past several decades.[6,7] Historically, cirrhosis has been associated with CLD due to hepatitis infections and alcohol-associated liver disease (ALD).[1] However, due to more effective therapies for hepatitis C and the rise in obesity levels, metabolic dysfunction–associated steatotic liver disease is becoming a leading cause of cirrhosis.[1,8]

In patients with cirrhosis, the metabolic and detoxifying abilities of the liver diminish, while fibrotic scarring can impair portal vein flow and increase hepatic resistance, leading to portal hypertension. The body compensates through the development of portosystemic collateral vessels and varices that bypass the heavily damaged liver.[1]

Patients remain generally asymptomatic during compensated cirrhosis. Initial decompensation is seen with the development of complications such as ascites, variceal hemorrhage, or hepatic encephalopathy (HE).[1,9]

Hepatic Encephalopathy

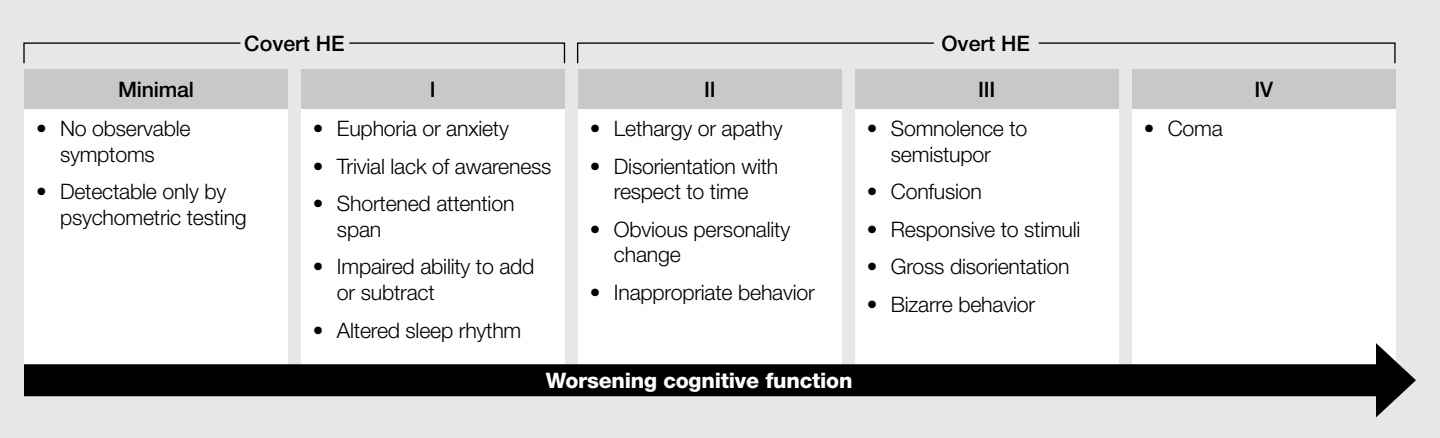
Up to 80% of patients with cirrhosis will develop HE.[2] Gut-derived neurotoxins (such as ammonia) that are normally broken down can instead accumulate in the brain due to hepatic insufficiency and/or portosystemic shunting.[1] Cirrhosis can also cause gut microbial imbalance (ie, dysbiosis), which is thought to be a major component of the pathophysiology of HE.[10] Ultimately, this causes inflammation, oxidative stress, swelling, and altered neurotransmission in the brain.[10,11]

The neuropsychiatric clinical manifestations of HE can be extremely heterogeneous. Symptoms can present anywhere on a continuum spanning from minimal cognitive deficits to extreme states of confusion, stupor, and coma.[2] The West Haven Criteria (also referred to as the Conn score) can be used to help classify patients with HE into stages or grades based on these symptoms (**Figure 1**).[2] The symptoms of covert HE may require specialized psychometric testing to detect, or may present as mild changes in overall mood, awareness, cognition, and sleep behavior.[2] The symptoms of overt HE (OHE) are more readily detectable and can be alarming, often requiring hospitalization to resolve an episode.[2,3] Patients with decompensated cirrhosis often experience recurrent OHE episodes, requiring proper management to reduce their frequency.[2]

Initial management of OHE requires identifying and controlling precipitating factors that may have initiated the episode.[2] These commonly include infections, gastrointestinal bleeds, constipation, dehydration, dietary factors, and/or the use of certain medications (eg, sedatives, opioids, diuretics).[2,12]

Nearly a third of patients hospitalized with HE are readmitted within 30 days of discharge, with a third of those patients readmitted due to HE.[13] Repeated hospitalizations decrease the likelihood of survival in patients with HE, making interventions that safely avoid rehospitalization a priority in the management of HE.[13,14]

Figure 1. West Haven Criteria (Conn Score)[2]



IMPORTANT SAFETY INFORMATION *(continued)*

- *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.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Rifaximin for the Reduction in Risk of OHE Recurrence

XIFAXAN® (rifaximin) is a nonsystemic antibiotic (<0.4% is absorbed from the gastrointestinal tract) that is FDA approved for the reduction in risk of OHE recurrence in adults. Rifaximin blocks one of the steps in the transcription of bacterial DNA to RNA, inhibiting protein synthesis and bacterial growth. It is administered as a twice-daily treatment course (550-mg tablet).[4]

The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) released joint practice guidelines in 2014 for the management of patients with HE. They recommend starting treatment for an OHE episode with the nonabsorbable disaccharide lactulose. Rifaximin earned the highest possible recommendation (GRADE I,A,1)* by the AASLD/EASL as an add-on therapy to lactulose to reduce the risk of OHE recurrence after a patient has a recurrence while on lactulose alone.[2]

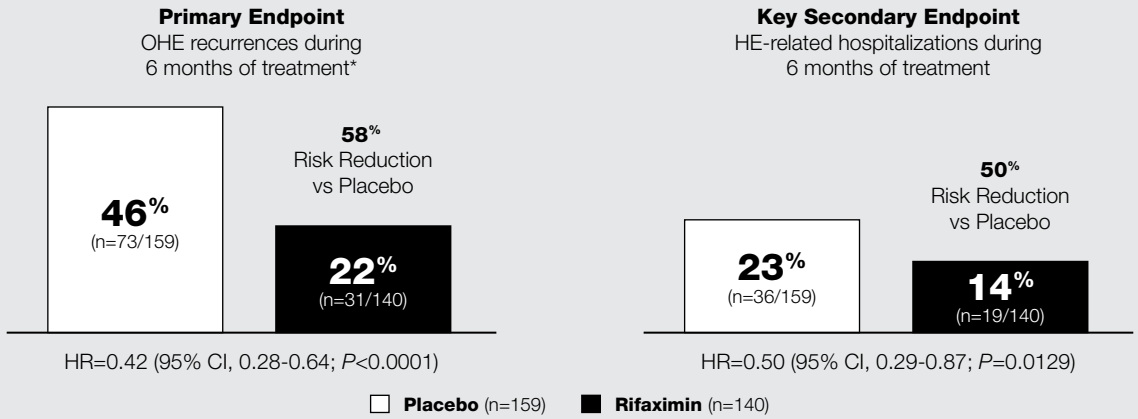
*Per the GRADE System for Evidence: Grade I=Randomized controlled trials; A=Evidence is "high quality," and further research is very unlikely to change our confidence in the estimated effect; and 1=Recommendation is "strong," with factors influencing strength of recommendation including the quality of evidence, presumed patient-important outcomes, and costs.[2]

Clinical Trials

The primary phase 3 study (Trial 1) assessed the efficacy and safety of XIFAXAN® (rifaximin) 550 mg twice daily compared to placebo over 6 months for the maintenance of OHE remission in adult patients with 2 or more prior OHE episodes associated with hepatic cirrhosis (N=299). A total of 91% of patients in both groups were also taking concomitant lactulose. Patients were withdrawn from the study after experiencing a breakthrough episode of OHE.[4,15]

The time to first breakthrough OHE episode during the 6-month treatment period was the primary endpoint in the trial. Twenty-two percent of patients (n=31/140) treated with rifaximin had an OHE recurrence, compared to 46% of those taking placebo (n=73/159; *P*<0.0001). This represents a 58% risk reduction in 6-month OHE recurrence. Similarly, results from the key secondary endpoint of HE-related hospitalization over the 6 months of treatment showed 14% of patients (n=19/140) on rifaximin required hospitalization, which was a significant 50% risk reduction compared to the 23% of those on placebo (n=36/159; *P*=0.0129) (**Figure 2**).[4,15]

Figure 2. Reduced Risk of 6-Month OHE Recurrence and HE-Related Hospitalization in Patients Taking Rifaximin Compared to Placebo[4,15]



91% of patients in each arm of the trial concomitantly used lactulose.

Primary endpoint: Time to first breakthrough OHE episode, defined as a marked deterioration in neurological function and an increase in Conn score to grade ≥2 or an increase in Conn score and asterixis grade of 1 each if patient entered study at grade 0.

- To prevent 1 OHE episode in 6 months with rifaximin plus background lactulose: **NNT = 4**

Key secondary endpoint: HE-related hospitalizations were defined as hospitalizations directly resulting from HE, or hospitalizations complicated by HE.

- To prevent 1 HE-related hospitalization in 6 months with rifaximin plus background lactulose: **NNT = 9**

*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.

NNT, number needed to treat.

The incidence of adverse events (AEs) was similar in the XIFAXAN® (rifaximin) and placebo treatment groups during the 6-month treatment period, with 80% of patients in each group experiencing ≥1 AE.[4,15] The most common AEs in Trial 1 are shown in **Table 1**.[4]

IMPORTANT SAFETY INFORMATION *(continued)*

- 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.

A separate open-label, active-controlled, multicenter, randomized study (Trial 2) compared the use of XIFAXAN® (rifaximin) 550 mg twice daily as monotherapy and in combination with lactulose over 6 months for the maintenance of OHE remission in patients with 1 or more prior OHE episodes associated with CLD (N=222). Breakthrough OHE episodes occurred in 25% (n=28/113) of the rifaximin monotherapy group and 14% (n=15/109) of the rifaximin with lactulose group during the 6-month treatment period. The most common AEs occurring in both treatment groups are shown in **Table 2**.[4]

Table 1. Common Adverse Reactions in ≥10% of Rifaximin-Treated Adult Patients With HE and Greater than Placebo (Trial 1)[4]

Adverse Reaction	Rifaximin 550 mg BID (n=140), n (%)	Placebo (n=159), n (%)
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%)

Adverse reactions that occurred in ≥5% but <10% of rifaximin-treated patients and greater than in patients who received placebo: muscle spasms, pruritus, abdominal pain, anemia, depression, nasopharyngitis, abdominal pain upper, arthralgia, dyspnea, pyrexia, and rash.

BID, twice daily.

Table 2. Common Adverse Reactions in ≥10% of Rifaximin-Treated Adult Patients With HE in Either Treatment Group (Trial 2)[4]

Adverse Reaction	Rifaximin 550 mg BID + Lactulose (n=108), n (%)	Rifaximin 550 mg BID Monotherapy (n=113), n (%)
Peripheral edema	15 (14%)	19 (17%)
Insomnia	15 (14%)	13 (12%)
Ascites	14 (13%)	8 (7%)
Diarrhea	13 (12%)	6 (5%)
Nausea	11 (10%)	17 (15%)
Muscle spasms	11 (10%)	9 (8%)
Constipation	9 (8%)	18 (16%)
Fatigue	9 (8%)	16 (14%)
UTI	9 (8%)	13 (12%)
Pruritis	6 (6%)	11 (10%)
Anemia	3 (3%)	11 (10%)

Adverse reactions that occurred in ≥5% but <10% of patients receiving rifaximin in either treatment group: dyspnea, anxiety, abdominal pain, decreased appetite, headache, cough, renal failure acute, and vomiting.

BID, twice daily; UTI, urinary tract infection.

Clinical Highlight #1: Real-World Evidence of Rifaximin Efficacy After an HE-Related Hospitalization

Disclaimer: *These results are based on observational claims data and are considered to have relevant limitations. Interpretation of the results is left to the intended audience.*

Arun Jesudian, MD

Dr. Arun Jesudian is a transplant hepatologist at New York-Presbyterian Hospital/Weill Cornell in New York City where he sees patients who have CLD in both inpatient and outpatient settings, including those with cirrhosis and HE. He notes that data suggest patients hospitalized with HE generally require a several-day hospitalization.[16] "In the beginning, patients have altered mental status, and our goal is to address the root cause of their HE episode."[2] Dr. Jesudian explains that, once precipitating factors are managed, discharge plans can be made; he also notes the importance of ensuring that the proper medication is being given.[2]

"These patients have a significantly higher risk of having another HE episode within a short period of time and ending up back in the hospital—we want to prescribe them medications to try and prevent further episodes."[2]

Dr. Jesudian takes time to have a detailed conversation with his patients and their caregivers about the admission, what causes or triggers HE, how HE is related to cirrhosis, and how medications like lactulose and XIFAXAN® (rifaximin) are important to help prevent future episodes. In line with the AASLD/EASL guideline for management of HE, Dr. Jesudian agrees the best care practice for someone hospitalized with HE while on lactulose is to add on rifaximin at discharge.[2]

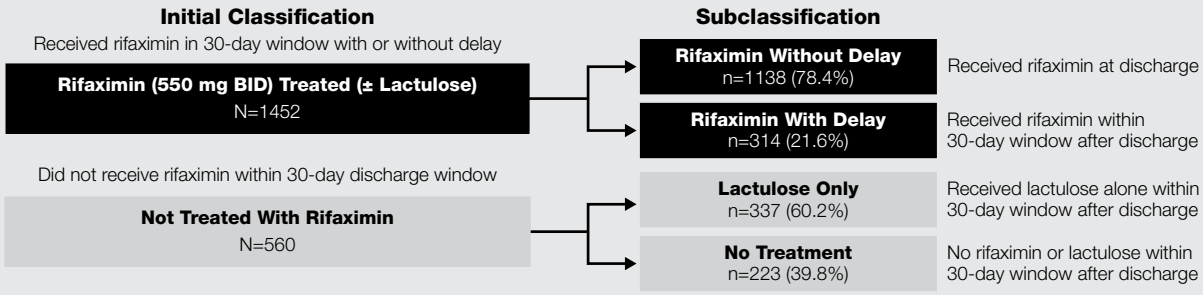
"You can find a lot of variability in how HE hospitalizations are managed—especially when there is a lack of gastroenterology or hepatology specialists readily available."

IMPORTANT SAFETY INFORMATION *(continued)*

- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Figure 3. Classification of Patients Based on Use of Rifaximin After Discharge[6]



BID, twice daily.

Dr. Jesudian notes that, alarmingly, some patients are discharged with no prophylactic therapy to prevent HE recurrence. "That's the most concerning group of patients (in my mind) because they really are set up to have rehospitalizations, which we know can impact patient outcomes significantly."[5] He explains that providers may have an educational gap about HE management, such as not being aware of HE recurrence and the need for prophylactic treatment as per the AASLD/EASL guideline.[2] In addition, some patients may run into access issues. "Once a patient leaves the hospital, prior authorization may delay them from receiving medication. Or in the worst-case scenario, it could lead to patients not taking the medication at all."

A recent study led by Dr. Jesudian examined real-world data on XIFAXAN® (rifaximin) and lactulose use after discharge and the subsequent rates of OHE-related rehospitalization and costs.[5] "The reason we conducted this study was because we recognized that patients who were admitted with HE and discharged were not always taking or filling prescriptions for lactulose and rifaximin, and we wanted to investigate whether any gap in these prophylactic therapies might be associated with readmission risk." The study used healthcare claims data focused on outpatient pharmacy claims from patients who were hospitalized due to an overt HE episode. Specifically, patients identified were 18-64 years old at the time of the hospitalization and had continuous health plan enrollment with ≥30 days of follow-up after hospitalization (N=2012).[5]

Identified patients were classified into 2 main groups depending on their access to rifaximin within 30 days of discharge, with 4 subgroups representing various levels of quality of care (**Figure 3**). "The first subgroup had access to rifaximin without any lapse after discharge. The second subgroup had access to rifaximin, but there was a lapse of less than 30 days where patients did not have it available to them. The third subgroup had access to lactulose within 30 days after discharge, but not to rifaximin (lactulose monotherapy). The fourth subgroup we would consider the lowest quality of care, who had access to neither lactulose nor rifaximin."[5]

Patients treated with XIFAXAN® (rifaximin) during the 30-day post-discharge period were less likely to have an OHE rehospitalization within 30 days vs patients not treated with rifaximin, adjusted for a priori selected potential confounding factors (6.8% vs 10.5%, respectively). Rifaximin-treated patients also had lower adjusted annual rates of OHE-related rehospitalizations compared to those patients not treated with rifaximin (0.7 vs 2.0, respectively) (**Figure 4**). "These data show a 44% lower risk of being rehospitalized with OHE within 30 days and a 59% lower annual rate of OHE rehospitalization if they received rifaximin (vs not receiving rifaximin)."[5] These results were then stratified and compared between subgroups based on quality of care. The patients in the subgroup who had direct access to rifaximin without any lapse in treatment had the lowest adjusted 30-day risk of OHE rehospitalization and also the lowest adjusted annual rate of OHE hospitalizations compared with the other subgroups.[5]

Dr. Jesudian's study also investigated the impact of rifaximin use on overall medical costs. "Providers need the full context of a treatment, including total costs to the patient. What we found is that, when comparing patients who did not receive rifaximin to patients who did receive rifaximin, we did not observe any difference in total annual healthcare costs."[5]

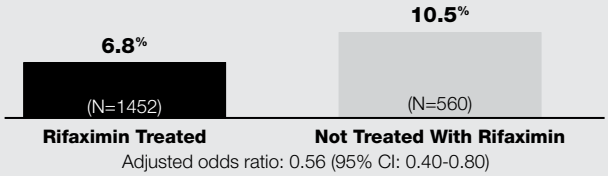
"The cost of rifaximin can be offset by avoiding hospitalizations, so the overall cost of care is not significantly different."[5]

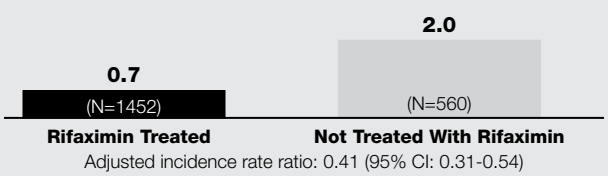
Results based on observational claims data are subject to common limitations, such as billing inaccuracies, omissions in coded claims, and limited clinical and laboratory information; outcomes may not be generalizable to all patients with cirrhosis. **Please see page 7 for a complete list of study limitations.** Overall, this study adds real-world evidence exploring the use of rifaximin in the reduction in risk of rehospitalization in patients after an OHE hospitalization.[5]

IMPORTANT SAFETY INFORMATION *(continued)*

- In clinical studies, the most common adverse reactions for XIFAXAN (alone or in combination with lactulose) were:
  - HE (≥10%): Peripheral edema (17%), constipation (16%), nausea (15%), fatigue (14%), insomnia (14%), ascites (13%), dizziness (13%), urinary tract infection (12%), anemia (10%), and pruritus (10%)

Figure 4. Adjusted 30-Day Risk and Annual Rate of OHE Rehospitalization After Discharge[5]





Limitations: Results are based on observational claims data and are subject to common limitations such as billing inaccuracies, omissions in coded claims, and limited clinical and laboratory information. Interpretation of the results is left to the intended audience.
Please see page 7 for a complete list of study limitations.

*Analyses were adjusted for a priori selected potential confounding factors associated with OHE hospitalizations and costs.

Clinical Highlight #2: Importance of Transition of Care in Patients With HE

Corrie Berk, DNP, MBA

Working as both an administrator and transplant hepatology nurse practitioner at the Texas Liver Institute in Austin, Dr. Corrie Berk primarily sees patients with cirrhosis in an outreach clinic setting. Many of these patients have decompensated cirrhosis with HE and often struggle daily dealing with their HE symptoms.[17,18]

"Patients with decompensated cirrhosis must balance their symptoms with new medications, frequent labs and appointments, and sometimes weekly paracentesis. Add in the cognitive issues from HE, and their burden increases."

Cirrhosis can affect a range of age groups with differing etiologies, bringing unique clinical challenges.[19] Patients younger than 40 years often have cirrhosis due to ALD and may still be struggling with alcohol use disorder that can further damage the liver and lead to decompensation, and potentially an HE episode.[1,19] On the other hand, older patients may have had HE symptoms misattributed as early signs of dementia, with a long journey to diagnosis of cirrhosis with HE.[2] "I have patients who carry a chart diagnosis of Alzheimer's disease, and we later find that all their cognitive changes were due to HE—which is manageable."

During an OHE episode, the primary goal in patient management is to identify and treat potential precipitating factors. Many of Dr. Berk's patients have had stable compensated cirrhosis become decompensated and cause HE due to dehydration, infections, certain medications, or gastrointestinal bleeds. In patients who have had prior OHE episodes and are having recurrent symptoms, Dr. Berk verifies with the patient and/or caregiver that lactulose is being administered properly and adds on XIFAXAN® (rifaximin) treatment if that hasn't been used previously.[2]

"Whoever is with the patient the most can tell you more than any lab value could about the patient's HE."

Caregivers are crucial in the management of HE, and Dr. Berk feels those patients who live alone tend to be most at risk for poor outcomes. Dr. Berk acknowledges the need for coordinated care between a patient's caregiver, primary care physician, and hepatologist, but notes that advanced practice providers (APPs) are crucial to help fill in access gaps.[2] "Studies have shown improved patient outcomes and quality of care with APP involvement in the patient's care team."[20] APPs and other providers can also help reduce HE recurrence in patients and improve patient outcomes by providing guidance on diet to prevent malnutrition and maintain nitrogen balance, monitoring renal health and electrolyte levels, and helping manage complications of cirrhosis that can precipitate an HE episode.[2]

Dr. Berk emphasizes the importance of educating patients and their caregivers about the medications they're taking and adherence. She makes sure patients are titrating lactulose to prevent dehydration, which can potentially precipitate another episode of HE.[2] For XIFAXAN® (rifaximin), Dr. Berk notes that it is important to ensure patients follow proper twice-daily dosing and stay adherent.[4]

Rifaximin is very well tolerated by Dr. Berk's patients, and she sees its efficacy being demonstrated in the responses of her patients, who often tell her how much rifaximin helps them. Dr. Berk encourages other clinicians to follow the AASLD/EASL guideline recommendations to use lactulose and rifaximin in patients at risk for OHE recurrence.[2]

"If you've practiced in cirrhosis management, you see first-hand that rifaximin reduces patients' risk of rehospitalization due to OHE."[5]

IMPORTANT SAFETY INFORMATION *(continued)*

- INR changes have been reported in patients receiving rifaximin and warfarin concomitantly. Monitor INR and prothrombin time. Dose adjustment of warfarin may be required.
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

 Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Limitations of the Jesudian 2023 Study[5]

- Claims data from commercially insured populations create unequal group sizes and may not be generalizable to all cirrhosis patients in the US and can contain billing inaccuracies or omissions in coded procedures, diagnoses, and pharmacy claims
- Claims data contain limited clinical and laboratory information; as such, it was not possible to observe inpatient medications nor obtain patients' cirrhosis severity (eg, MELD score, Child-Pugh grades)
- Information on mortality was not available and survival could not be assessed
- Despite adjustments for baseline characteristics in OHE hospitalization and cost comparisons, residual selection bias and confounding may have remained
- Due to the lack of a specific ICD-10-CM diagnosis code for HE at the time the analyses were conducted, patients with HE were identified using an algorithm developed based on medical expert input
- Total healthcare costs were reported from a payer's perspective, which do not capture indirect costs associated with the patient burden
- Challenges associated with approximating medication adherence are a known limitation of using claims data
  - For the purposes of this study, adherence was assumed to have been complete
- Due to the retrospective design of the study, no causality can be established

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.
- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin.
- In clinical studies, the most common adverse reactions for XIFAXAN (alone or in combination with lactulose) were:
  - HE (≥10%): Peripheral edema (17%), constipation (16%), nausea (15%), fatigue (14%), insomnia (14%), ascites (13%), dizziness (13%), urinary tract infection (12%), anemia (10%), and pruritus (10%)
- INR changes have been reported in patients receiving rifaximin and warfarin concomitantly. Monitor INR and prothrombin time. Dose adjustment of warfarin may be required.
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

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.

Please click here for full Prescribing Information.

REFERENCES

1. Garcia-Tsao G. Cirrhosis and its sequelae. In: Goldman L et al, eds. *Goldman-Cecil Medicine*. 26th ed. Elsevier; 2016:990-998.e3. **2.** Vilstrup H et al. *Hepatology*. 2014;60(2):715-735. **3.** Bajaj JS et al. *Clin Gastroenterol Hepatol*. 2017;15(4):565-574.e4. **4.** XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals. **5.** Jesudian AB et al. *J Med Econ*. 2023;26(1):1169-1177 [published correction appears in *J Med Econ*. 2023;26(1):1356]. **6.** Orman ES et al. *JAMA Netw Open*. 2019;2(6):e196412 [published correction appears in *JAMA Netw Open*. 2019;2(10):e1913673]. **7.** Moon AM et al. *Clin Gastroenterol Hepatol*. 2020;18(12):2650-2666. **8.** Rinella ME et al. *J Hepatol*. 2023;79(6):1542-1556. **9.** Garcia-Tsao G et al. *Hepatology*. 2017;65(1):310-335. **10.** Bajaj JS et al. *Am J Physiol Gastrointest Liver Physiol*. 2012;302(1):G168-G175. **11.** Häussinger D, Görg B. Oxidative/nitrosative stress and hepatic encephalopathy. Chapter 32. In: Sies H, ed. *Oxidative Stress: Eustress and Distress*. Academic Press; 2020:669-693. **12.** Pantham G et al. *Dig Dis Sci*. 2017;62(8):2166-2173. **13.** Kruger AJ et al. *Ann Hepatol*. 2019;18(2):310-317. **14.** Tapper EB et al. *Aliment Pharmacol Ther*. 2020;51(12):1397-1405. **15.** Bass NM et al. *N Engl J Med*. 2010;362(12):1071-1081. **16.** Orr JG et al. *Liver Int*. 2016;36(9):1295-1303. **17.** Moscucci F et al. *Liver Int*. 2011;31(10):1505-1510. **18.** Bajaj JS et al. *Am J Gastroenterol*. 2011;106(9):1646-1653. **19.** Sajja KC et al. *J Investig Med*. 2014;62(7):920-926. **20.** Tapper EB et al. *Hepatology*. 2020;71(1):225-234.

SPECIAL REPORT

Salix Pharmaceuticals

Salix Pharmaceuticals, 400 Somerset Corporate Blvd., Bridgewater, NJ 08807