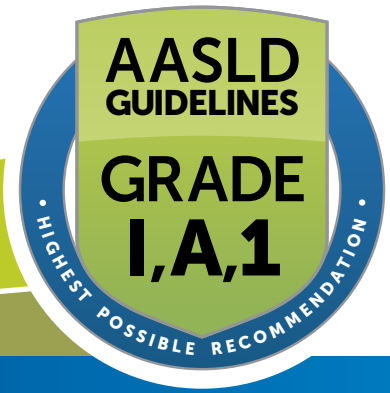
IDENTIFY PATIENTS AT RISK OF OVERT HEPATIC ENCEPHALOPATHY (OHE) RECURRENCE AND ACT WITH GUIDELINE-BASED CARE

R.O.A.R. AGAINST OHE

***R**ecognize the risks*
***O**bserve the patient's symptoms*
***A**lign with the AASLD guidelines*
***R**educe the risk of recurrence*



XIFAXAN earned the highest possible recommendation (GRADE I,A,1) by 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.[1,*]

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver.

*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.[1]

INDICATION

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

IMPORTANT SAFETY INFORMATION

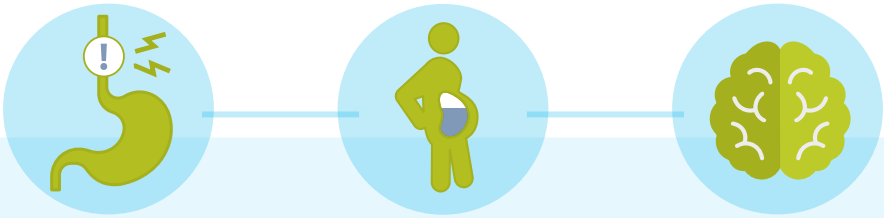
- XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

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

Xifaxan®
rifaximin 550 mg tablets

R. *Recognize the risks*

Patients with chronic liver disease/ decompensated cirrhosis who have portal hypertension have a higher risk of complications, such as[2,3]



Varices **Ascites** **HE**

HE is a primary complication of cirrhosis[1]

UP TO 80%

of patients with cirrhosis will eventually develop some form of HE.[1]

Because decompensation places patients at higher risk for additional complications of cirrhosis—including death—screening for each potential symptom is critical for guideline-based care.[3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

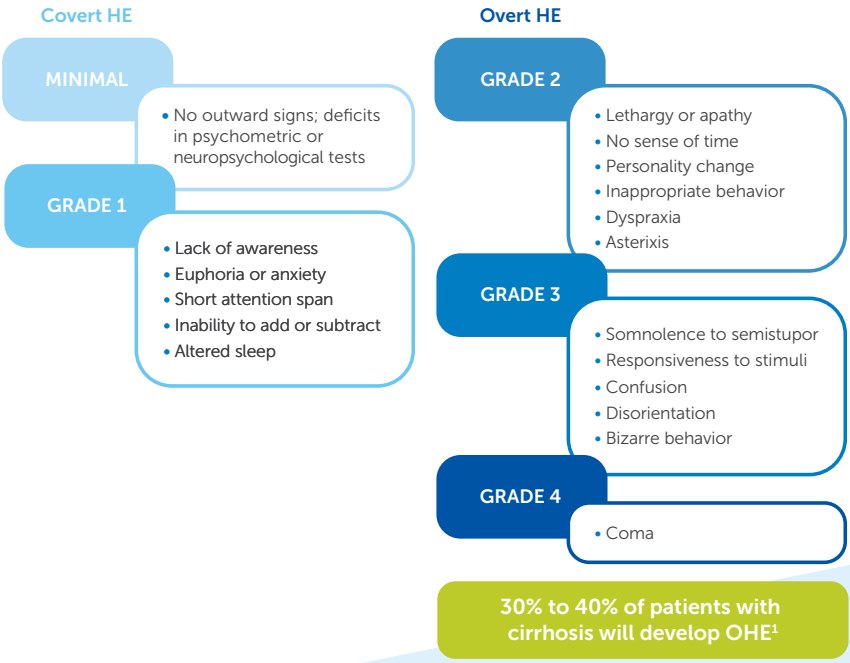
- XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

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

0. Observe the patient's symptoms

Diagnosing OHE is a decision based on clinical examination, requiring the detection of signs suggestive of HE in patients with severe liver insufficiency who do not have obvious alternative causes of brain dysfunction (eg, certain medications, metabolic deficiencies, or other medical conditions).[1]

Use the West Haven criteria as your gold standard for classifying HE[1]



What does an HE episode look like?

Your patients may not exhibit outward signs of HE at the time of their appointment. Therefore, it's important to ask whether they've experienced any of the symptoms listed in the West Haven criteria during the time leading up to their visit, rather than just in that moment. If they answer in the affirmative, it may be time to act.

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.
- 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.

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

A. Align with the AASLD guidelines

General recommendations for the treatment of OHE include actively treating current episodes (GRADE II-2,A,1), offering secondary prophylaxis after an episode occurs (GRADE I,A,1), and providing primary preventative treatment for patients with cirrhosis with a known high risk of developing HE (GRADE II-3,C,2).[1,*]

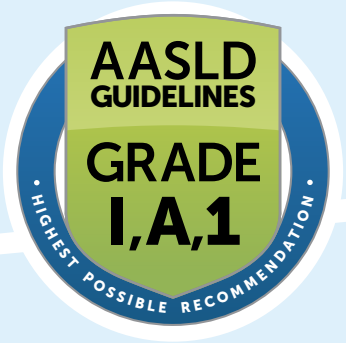
XIFAXAN earned the highest possible recommendation (GRADE I,A,1) by AASLD/EASL as an add-on therapy to lactulose for the reduction in risk of OHE recurrence.[1,*]

XIFAXAN has shown to be an effective way to reduce the risk of OHE recurrence.[4] Lactulose may not always be sufficient when used alone.[1,5]

What do the guidelines say about ammonia?

Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease. A normal value calls for diagnostic reevaluation (GRADE II-3,A,1).[1,*]

* Per the GRADE System for Evidence: Grade I=randomized, controlled trials; II-2=cohort or case-control analytic studies; II-3=multiple time series, dramatic uncontrolled experiments; A=evidence is "high quality," and further research is very unlikely to change our confidence in the estimated effect; C=evidence is "low quality," and further research is likely to have an important impact on confidence in the estimate effect and is likely to change the estimate. Any change of estimate is uncertain; 1=recommendation is "strong," with factors influencing strength of recommendation including the quality of evidence, presumed patient-important outcomes, and costs; 2=recommendation is "weak," with variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher costs, or resource consumption.[1]



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.
- 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%)

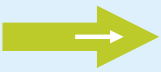
Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Reduce the risk of recurrence

Ensuring your patients are prescribed guideline-based therapy can help reduce the risk of future OHE episodes,[4] but there are additional steps you can take as well.

Open the lines of communication: Patients with OHE may pose a severe risk to themselves and others. Ensure everyone involved with your patients' care (eg, caregivers and clinicians) understands the dangers of not filling and taking their medication

Classify their disease accurately: The ICD-10 code for OHE is **K76.82** (hepatic encephalopathy; indicate lactulose history if applicable)[6,†]



Simplify the PA process: Initiate PAs in office instead of awaiting pharmacy initiation to help increase dispense rate[6]

[†]As of 2022. The ICD-10 code and all other patient-access–related information are provided for informational purposes only. It is the treating physician's responsibility to determine the proper diagnosis, treatment, and applicable ICD-10 code. Salix Pharmaceuticals does not guarantee coverage or reimbursement for the product.

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.

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.

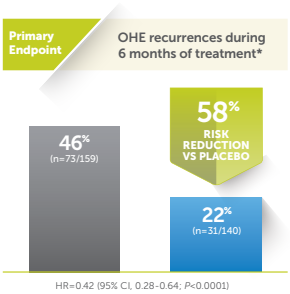
Xifaxan® rifaximin 550 mg tablets

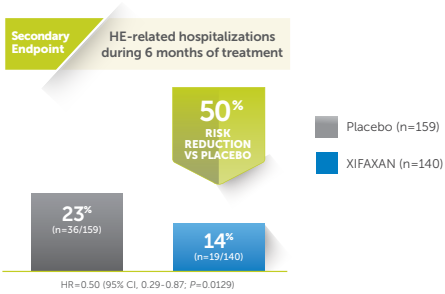
Please see additional Important Safety Information throughout and click here for full Prescribing Information.

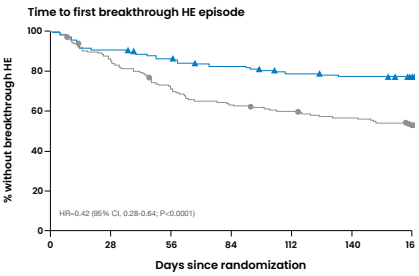
R.O.A.R. against OHE

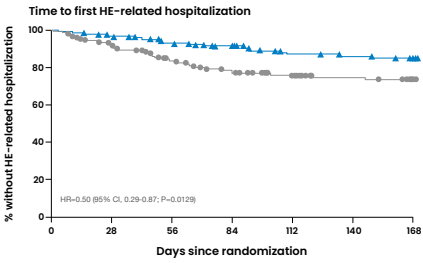
According to AASLD guidelines, XIFAXAN is an effective add-on therapy to lactulose to reduce the risk of OHE recurrence.[1] But XIFAXAN is only 1 important step. Identify potential patients and watch out for OHE symptoms. **ROAR against OHE.**

XIFAXAN cut the risk of OHE recurrence and HE-related hospitalizations in half[4,7]









91% of patients in the placebo and XIFAXAN groups were on lactulose[4,7]

*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.

Study design[4,7]

- In a randomized, placebo-controlled, double-blind, multicenter, multinational, 6-month study, the efficacy of XIFAXAN 550 mg (taken orally twice a day) was evaluated in 299 adult patients
- **Inclusion criteria:** Currently in remission (Conn score of 0 or 1) from HE and ≥2 episodes of HE associated with chronic liver disease in the previous 6 months
- **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
- **Key secondary endpoint:** HE-related hospitalization

AASLD GUIDELINES GRADE I,A,1 · HIGHEST POSSIBLE RECOMMENDATION ·

Prescribe guideline-recommended XIFAXAN for your patients at risk of OHE recurrence. **Learn more at XIFAXAN.com.**

Xifaxan® rifaximin 550 mg tablets

A demonstrated safety profile[4]

Trial 1 safety data (occurring in ≥10% of patients)

Common Adverse Reactions	XIFAXAN (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 patients receiving XIFAXAN and greater than in patients who received placebo: muscle spasms, pruritus, abdominal pain, anemia, depression, nasopharyngitis, abdominal pain upper, arthralgia, dyspnea, pyrexia, and rash.

Trial 2 safety data (occurring in ≥10% of patients)*

Common Adverse Reactions	XIFAXAN + lactulose (N=108), n (%)	XIFAXAN (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%)**
Urinary tract infection	**9 (8%)**	**13 (12%)**
Pruritus	**6 (6%)**	**11 (10%)**
Anemia	**3 (3%)**	**11 (10%)**

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

*Trial 2 safety data described in Table 2 reflect randomized patient exposure to XIFAXAN + lactulose or XIFAXAN monotherapy in an open-label, active-controlled, multicenter, 6-month trial in adults with hepatic encephalopathy.

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

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. 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. **2.** Mansour D, McPherson S. Management of decompensated cirrhosis. *Clin Med (Lond).* 2018;18(suppl 2):s60-s65. **3.** Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2017;65(1):310-335. **4.** XIFAXAN. Prescribing information. Salix Pharmaceuticals; 2022. Accessed May 19, 2023. https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf **5.** Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology.* 2010;138(7):2332-2340. **6.** Data on file. XIFAXAN CMM Executive Summary 2022. Salix Pharmaceuticals, Bridgewater, NJ. **7.** Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071-1081.

Salix Pharmaceuticals, 400 Somerset Corporate Blvd., Bridgewater, NJ 08807
The XIFAXAN 550 mg product and the XIFAXAN trademark are licensed by Alfasigma S.p.A. to Salix Pharmaceuticals or its affiliates.

Salix Pharmaceuticals