FOLLOW GUIDELINE-RECOMMENDED CARE FOR YOUR ADULT PATIENTS AT RISK OF OVERT HEPATIC ENCEPHALOPATHY (OHE) RECURRENCE[1]

Xifaxan®
rifaximin 550 mg tablets

Prescribe XIFAXAN after an OHE episode, the only FDA-approved agent indicated for the

REDUCTION IN RISK OF OHE RECURRENCE IN ADULTS[2,3]

AASLD GUIDELINES
GRADE I,A,1
HIGHEST POSSIBLE RECOMMENDATION

XIFAXAN 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.[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.

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

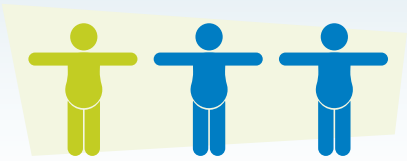
*Per the GRADE System for Evidence: Grade I=randomized, controlled trials; A=evidence is "high quality," and further research is very unlikely to change our confidence in the estimated effect; and 1=recommendation is "strong," with factors influencing strength of recommendation including the quality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

Overt hepatic encephalopathy (OHE) is a complication of cirrhosis[4]

Patients with CLD/decompensated cirrhosis who have portal hypertension have a higher risk of complications, such as varices, ascites, and HE[5,6]

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

of patients with cirrhosis have an OHE episode during their disease course[1]



Nearly 1 in 3 patients with cirrhosis hospitalized with HE were readmitted within 30 days[7,*] (n=7931/24,473)

Multiple episodes of OHE can lead to persistent cognitive deficits in[8]:

Working memory — Response inhibition — Reaction time — Attention span

Repeated hospitalizations decrease the likelihood of survival[7,9]

The 1-year survival of patients with cirrhosis decreases from 83% to 36% with an OHE diagnosis[10,†]

While lactulose is generally used for initial OHE therapy, it may not always be sufficient when used alone[1]

- AASLD/EASL guidelines raise points to keep in mind regarding lactulose monotherapy to reduce the risk of OHE recurrence
  - In one study, subjects with a previous episode of OHE were found to have a 40% cumulative risk of recurring OHE at 1 year, and subjects with recurrent OHE have a 40% cumulative risk of another recurrence within 6 months, despite lactulose treatment

AASLD, American Association for the Study of Liver Diseases; CLD, chronic liver disease; EASL, European Association for the Study of the Liver; HE, hepatic encephalopathy.

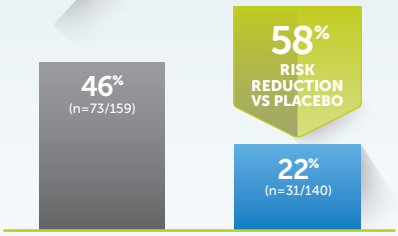
*Study utilized the 2013 Nationwide Readmission Database (NRD; represented about 49% of the US population and all hospitalizations) and focused particularly on hospitalized patients with HE (n=24,473) to assess independent predictors of 30-day readmission and develop a readmission risk model in patients with HE. The impact of 30-day readmission in patients with HE on calendar-year mortality were also assessed. **Limitations:** The NRD does not provide information based on race, ethnicity, severity of HE, or laboratory parameters. MELD scores were unavailable, so a misclassification error is possible. Medications and other treatment goals (lactulose and bowel movement frequency) were not recorded. Information on mortality outside of hospital admission was not available (the reported mortality may have been underrepresented in the study).[7]

†Data from 3 Danish healthcare registries of patients with cirrhosis due to alcohol use disorder and not previously examined for suspected cirrhosis (N=466) diagnosed between January 1, 1993, and August 31, 2005. The diagnosis of HE was based on the patient's clinical presentation, usually supported by the blood ammonia level and/or a continuous reaction time. Minimal HE was excluded. Values represent survival probabilities after diagnosis of the complication, with or without development of additional complications.[10]

XIFAXAN cut the risk of OHE recurrence and HE-related hospitalizations in half[3,11]

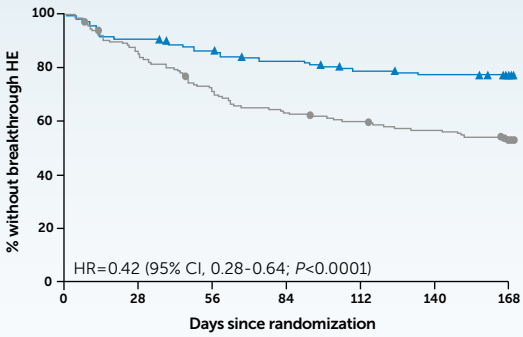
In a clinical trial of adults with OHE[3,11]

Primary Endpoint — OHE recurrences during 6 months of treatment*



HR=0.42 (95% CI, 0.28-0.64; *P*<0.0001)

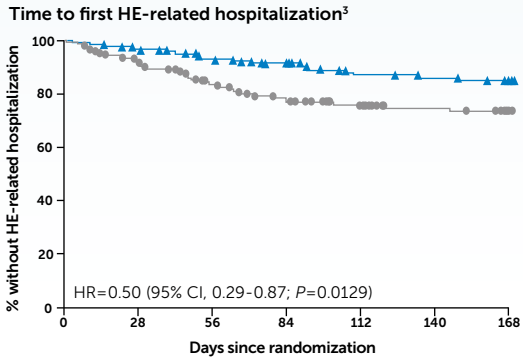
Time to first breakthrough HE episode[3]



Secondary Endpoint — HE-related hospitalizations during 6 months of treatment†

HR=0.50 (95% CI, 0.29-0.87; *P*=0.0129)

Time to first HE-related hospitalization[3]



Placebo (n=159) XIFAXAN (n=140)

91% of patients in the placebo and XIFAXAN groups were on lactulose[3,11]

Study design[3,11]

- 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

*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.[3]

†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.[3]

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.

Xifaxan® rifaximin 550 mg tablets

XIFAXAN has a demonstrated safety profile[3]

Trial 1 safety data (occurring in ≥10% of patients)[3]

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)[3,*]

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.[3]

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.
- 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.

Xifaxan® rifaximin 550 mg tablets

XIFAXAN should be initiated in all appropriate adults with OHE to help reduce the risk of recurrence[1]

Continuity of care is critical in patients with OHE given the high risk of recurrence[1]

XIFAXAN is an easy-to-implement medication for your adult patients at risk of OHE recurrence[3]

rfx

One 550-mg tablet twice daily—no dose adjustments or titrations needed[3]

- 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

Can be taken **with or without food**[3]

Can be continued for as long as patient is at risk of recurrent OHE[3]

K76.82

When prescribing XIFAXAN, use the ICD-10 code for OHE: **K76.82** (Hepatic encephalopathy; indicate lactulose history if applicable)[12,*]

*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*)

- 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.

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

Xifaxan® rifaximin 550 mg tablets

XIFAXAN has excellent insurance coverage when the prescription is written correctly[13]

Prior Authorizations (PAs) are common. To avoid gaps in care, initiate PAs in office vs awaiting pharmacy initiation when necessary

In general, PAs proactively generated by prescribers had a higher dispense rate than PAs initiated by pharmacies[14]

When a PA is required, complete the following steps:

- **STEP 1 — Provide patient and insurance information**
- **STEP 2 — Include prescriber information**
  (eg, practice name, your name, NPI #, DEA/License #)
- **STEP 3 — Provide accurate information, including:**
  - **Age, diagnosis, dosing**
    Age of patient, twice daily, 60 tablets with refills[3,]*
  - **ICD-10 code for OHE[12,†]**
    K76.82 *Hepatic Encephalopathy. Indicate lactulose history if applicable.*
  - **Previous therapies tried and failed**
    (eg, lactulose)
  - **Rationale for prescribing XIFAXAN**
    (eg, breakthrough OHE episode while on lactulose)
- **STEP 4 — Remember your signature and the date**

Remember to check for accurate and complete prescribing in EHR/EMR and on Rx, and consider XIFAXAN 550 mg for your system's EHR preference list or favorites. For PA support for XIFAXAN, go to **covermymeds.com** or call **1-866-452-5017**.

*If coverage allows refills, write for 180 tablets.
†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.

Access additional resources

XIFAXAN Copay Card

OHE clinical tools and educational resources

IMPORTANT SAFETY INFORMATION (*continued*)

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

References: 1. Vilstrup H et al. *Hepatology*. 2014;60(2):715-735. **2.** Shawcross DL et al. *Eur J Gastroenterol Hepatol*. 2016;28(2):146-152. **3.** XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals. **4.** Garcia-Tsao G. Cirrhosis and its sequelae. In: Goldman L et al, eds. *Goldman-Cecil Medicine*. 26th ed. Elsevier; 2016:990-998.e3. **5.** Garcia-Tsao G et al. *Hepatology*. 2017;65(1):310-335. **6.** Mansour D, McPherson S. *Clin Med (Lond)*. 2018;18(Suppl 2):s60-s65. **7.** Kruger AJ et al. *Ann Hepatol*. 2019;18(2):310-317. **8.** Bajaj JS et al. *Gastroenterology*. 2010;138(7):2332-2340. **9.** Sood KT, Wong RJ. *J Clin Exp Hepatol*. 2019;9(4):484-490. **10.** Jepsen P et al. *Hepatology*. 2010;51(5):1675-1682. **11.** Bass NM et al. *N Engl J Med*. 2010;362(12):1071-1081. **12.** CMS. 2024 ICD-10-CM. Accessed April 30, 2024. https://www.cms.gov/medicare/coding-billing/icd-10-codes/2024-icd-10-cm **13.** Data on file. MMIT September 2023. Salix Pharmaceuticals, Bridgewater, NJ. **14.** Data on file. XIFAXAN CMM Executive Summary 2022. Salix Pharmaceuticals, Bridgewater, NJ.

Salix Pharmaceuticals

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