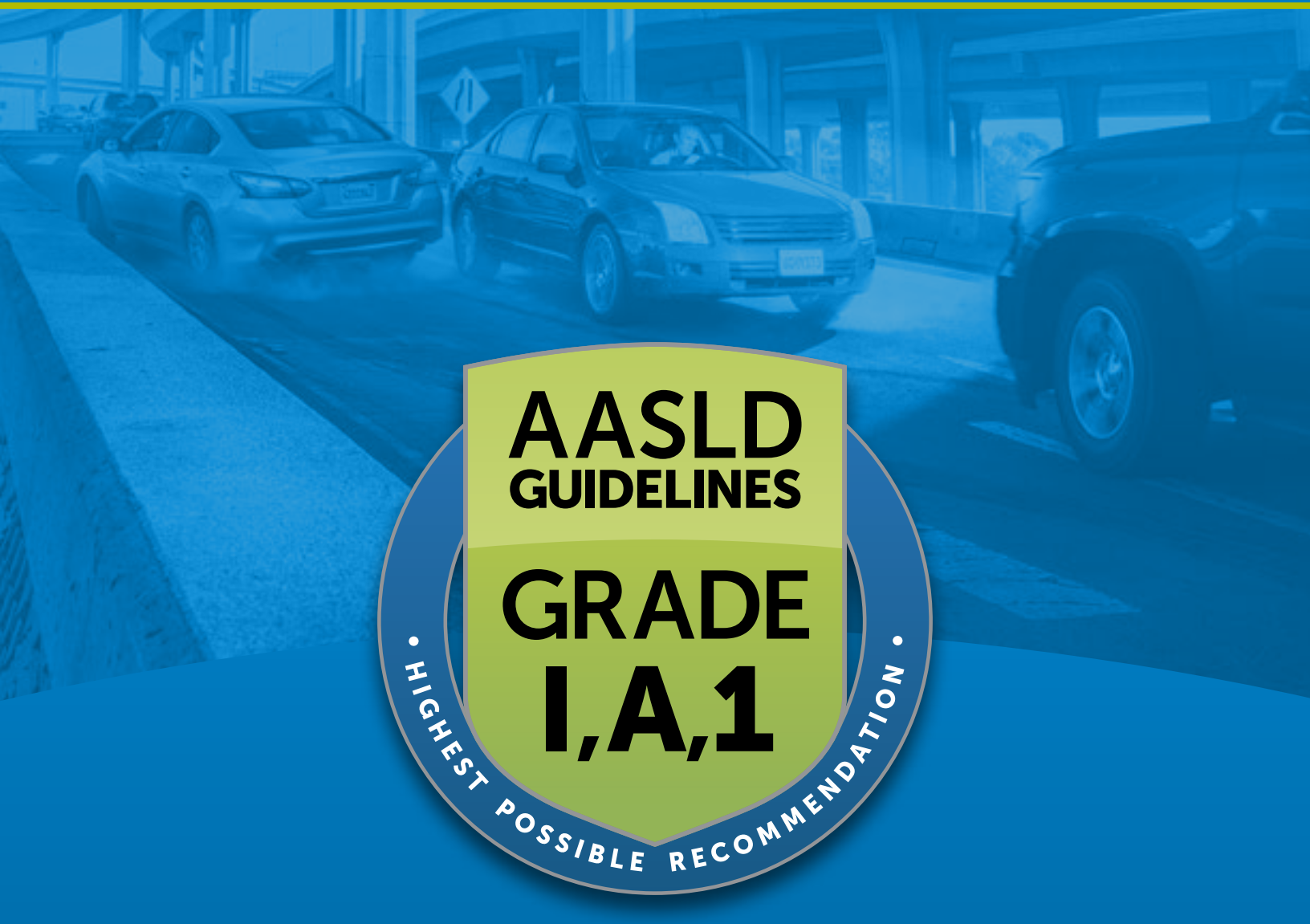
Align with the guidelines for patients at risk for overt hepatic encephalopathy (OHE) recurrence



XIFAXAN earned AASLD's highest possible recommendation* (GRADE I,A,1) 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® 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 accompanying full Prescribing Information.

AASLD=American Association for the Study of Liver Diseases

*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.

Xifaxan® rifaximin 550 mg tablets

About the AASLD Guidelines

The mission of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) is to advance the practice of hepatology and promote liver health.[2] As part of this mission, AASLD/EASL publishes data-supported practice guidelines to disseminate the science of hepatology and support quality patient care.[2]

Diagnosing and grading severity of OHE

Diagnosing OHE is a clinical decision based on a clinical examination, requiring the detection of signs suggestive of HE in a patient with severe liver insufficiency and/or portosystemic shunts who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors for HE (eg, GI bleeding and infections) supports the diagnosis of HE.[1]

West Haven criteria for HE (including minimal HE)[1]

Minimal	Stage 1	Stage 2	Stage 3	Stage 4
• No outward signs; deficits in psychometric or neuro-psychological tests	• Lack of awareness • Euphoria or anxiety • Short attention span • Can't add or subtract • Altered sleep	• Lethargy/apathy • No track of time • Personality change • Inappropriate behavior • Dyspraxia • Asterixis	• Somnolence to semi-stupor • Responsive to stimuli • Confused • Disoriented • Bizarre behavior	• Coma
		30-40% of cirrhosis patients will develop overt (clinically apparent) HE[1]		

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).*
>
> **–Recommendation 9**

References: 1. American Association for the Study of Liver Diseases. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by AASLD and EASL. https://www.aasld.org/sites/default/files/2019-06/141022_AASLD_Guideline_Encephalopathy_4UFd_2015.pdf. Accessed April 20, 2020. **2.** Our story. American Association for the Study of Liver Diseases website. https://aasld.org/about-aasld/our-story. Accessed February 21, 2020. **3.** XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals. **4.** Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071-1081.

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 accompanying full Prescribing Information.

Managing OHE

"Secondary prophylaxis after an episode for OHE is recommended (GRADE I,A,1)."

–Recommendation 11

I,A,1 is the highest possible recommendation by both AASLD and EASL[1]

XIFAXAN® (rifaximin) earned AASLD/EASL's highest possible recommendation (GRADE I,A,1) 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]

Per the GRADE System for Evidence*:

GRADE I: Proven in randomized, controlled trials[1]

GRADE A: Evidence is "high quality," and further research is very unlikely to change our confidence in the estimated effect[1]

GRADE 1: Recommendation is "strong," with factors influencing strength of recommendation including the quality of evidence, presumed patient-important outcomes, and costs[1]

Transition from inpatient care to home care

Ongoing management and team awareness post-discharge is recommended, including educating the patient, caregivers, and providers so that everyone on the care team understands how to manage HE and reduce the risk of repeated HE-related hospitalizations.[1]

*The GRADE system for evidence: I=Randomized, controlled trials, II-1=Controlled trials without randomization, II-2=Cohort or case-control analytic studies, II-3=Multiple time series, dramatic uncontrolled experiments, III=Opinions of respected authorities, descriptive epidemiology; A=High quality: Further research is very unlikely to change our confidence in the estimated effect, B=Moderate: Further research is likely to have an important impact on our confidence in the estimated effect and may change the estimate, C=Low quality: Further research is likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate. Any change of estimate is uncertain; 1=Strong: Factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes, and costs, 2=Weak: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher costs, or resource consumption.

IMPORTANT SAFETY INFORMATION *(continued)*

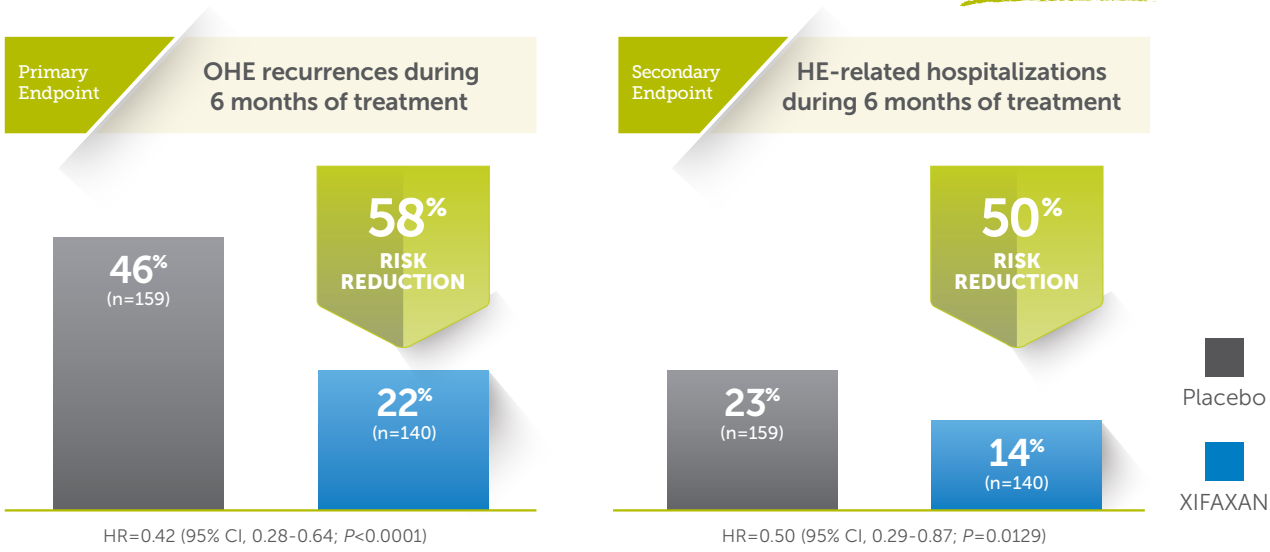
- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential 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 accompanying full Prescribing Information.

AASLD: XIFAXAN is an effective add-on therapy to lactulose to reduce the risk of overt hepatic encephalopathy (OHE) recurrence[1,3]

In a clinical trial of adults

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



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

Study design[3,4]

- 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 subjects
- **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 (an increase in Conn score to grade ≥2 or an increase in Conn score and asterixis grade of 1 each if subject entered study at grade 0)
- **Key secondary endpoint:** HE-related hospitalization

INDICATION

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

IMPORTANT SAFETY INFORMATION *(continued)*

- In a clinical study, the most common adverse reactions for XIFAXAN in HE (≥10%) were peripheral edema (15%), nausea (14%), dizziness (13%), fatigue (12%), and ascites (11%).
- 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 see additional Important Safety Information throughout and accompanying full Prescribing Information.

Learn more about XIFAXAN and the AASLD Guidelines at **XIFAXAN.com/AASLD**

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Xifaxan® rifaximin 550 mg tablets