From: <<noreply@salix.com>>

To: {{recipient name and email}}

Subject:

1. Recognize patients at risk of overt HE
2. Insight on a common complication of CLD/cirrhosis
3. When to screen for overt HE

Preheader:

1. Learn about this growing problem
2. Why this first step is so critical
3. What to screen for early
4. Discover the impact of CLD/cirrhosis

https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf

Xifaxan (rifaximin) 550 mg tablets

Full Prescribing Information | Important Safety Information

FOR THE REDUCTION IN RISK OF OVERT HEPATIC ENCEPHALOPATHY (OHE) RECURRENCE IN ADULTS[1]

Chronic liver disease (CLD) and cirrhosis are a growing problem

Dear {{accFname}} {{accLname}},

CLD and cirrhosis are a growing problem.[2] In fact, among patients aged 25 to 54, CLD and cirrhosis have a greater mortality than diabetes or cerebrovascular disease.[3] Additionally, up to 40% of patients with cirrhosis will develop OHE.[4] Read on and click below to learn more.

Learn more about CLD and OHE—and how to identify patients at risk of OHE

https://www.xifaxan.com/siteassets/hehcp/pdf/xifaxan-he-aasld-guidelines-update.pdf

Get Started >

SELECT 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 below.

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

Varices | Ascites | HE

HE is a primary complication of cirrhosis. Up to **80% of patients** with cirrhosis will eventually develop some form of HE. And **30% to 40% of patients** will develop overt HE (OHE), with a high risk of recurrence, despite lactulose treatment.[4]

XIFAXAN can help by reducing the risk of OHE recurrence in adults.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

- *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.

https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

INDICATION

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

Please click here for full Prescribing Information.

https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf

AASLD GUIDELINES GRADE I,A,1

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.[41]

Proactive screening for HE is critical for patients with CLD/cirrhosis.[6,7] Even if they exhibit no obvious causes of brain dysfunction, identifying symptoms of HE early is key.[7]

Help patients at risk of overt HE recurrence—screen early

https://www.xifaxan.com/siteassets/hehcp/pdf/xifaxan-he-aasld-guidelines-update.pdf

Download the AASLD Guidelines >

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.

References: 1. XIFAXAN. *Prescribing Information*. Salix Pharmaceuticals; 2023. **2.** Hirode G, Saab S, Wong RJ. Trends in the burden of chronic liver disease among hospitalized US adults. JAMA Netw Open. 2020;3(4):e201997. doi:10.1001/jamanetworkopen.2020.1997. **3.** Xu J, Murphy SL, Kochanek KD, Arias E. Deaths: final data for 2019. *Nat Vital Stat Rep*. 2021;70(8):1-87. doi:10.15620/cdc:106058. **4.** 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. doi:10.1002/hep.27210. **5.** Mansour D, McPherson S. Management of decompensated cirrhosis. *Clin Med* (Lond). 2018;18(suppl 2):s60-s65. doi:10.7861/clinmedicine.18-2-s60 **6.** 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. doi:10.1002/hep.28906. **7.** Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol*. 2001;96(9):2718-2723.

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