Gastroenterologists

REDUCE THE REPEAT

Disrupt the pattern of overt hepatic encephalopathy (OHE) episodes with XIFAXAN[1]

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.[2,*]

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 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.[2]

Xifaxan® rifaximin 550 mg tablets

CHRONIC LIVER DISEASE (CLD) AND CIRRHOSIS ARE A GROWING PROBLEM[3]

Diabetes/cerebrovascular disease (stroke)

CLD and cirrhosis had **greater mortality in patients aged 25 to 54** than diabetes or cerebrovascular disease (2019)[4]

CLD and cirrhosis were the **9th leading cause of death** in the US in 2021[5]

45% increase in total number of CLD-related hospitalizations from 2005 to 2017[6,*]

*Rates per 1000 persons.

Patients with CLD/decompensated cirrhosis who have portal hypertension have a higher risk of complications, such as[7,8]:

Varices

Ascites

HE

HE is a primary complication of cirrhosis[2]

UP TO 80%

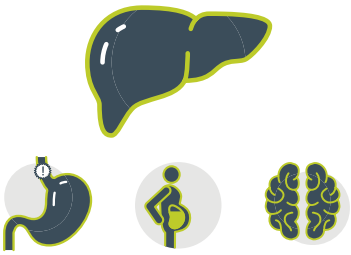
of patients with cirrhosis will eventually develop some form of HE[2]

HE classification using the West Haven criteria (including minimal HE)[2]

Covert HE		Overt HE		
MINIMAL	GRADE 1	GRADE 2	GRADE 3	GRADE 4
• No outward signs; deficits in psychometric or neuropsychological tests	• Lack of awareness • Euphoria or anxiety • Short attention span • Inability to add or subtract • Altered sleep	• Lethargy/apathy • No sense of time • Personality change • Inappropriate behavior • Dyspraxia • Asterixis	• Somnolence to semistupor • Responsiveness to stimuli • Confusion • Disorientation • Bizarre behavior	• Coma

30% to 40% of patients with cirrhosis will develop OHE[2]

AASLD guidelines for cirrhosis and portal hypertension include management of[8,9]:



Compensated cirrhosis shows little or no outward signs of disease. Decompensation occurs when overt cirrhosis symptoms are present, such as development of encephalopathy, ascites, and/or gastrointestinal bleeding due to portal hypertension. **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.[8]**

Considerations when evaluating a patient for HE[2,8,10,*]

Procedures

- Upper endoscopy
  - Variceal surveillance
  - Variceal ligation
- General GI surgery
- Paracentesis of ascites
- TIPS placement
- Abdominal echo

Diagnoses

- Decompensated cirrhosis
- Portal hypertension
- Portal vein thrombosis
- Thrombocytopenia

Management

- Opioids
- Anti-infectives
- Beta blockers
- Potassium-sparing and loop diuretics
- Certain antidepressants
- Electrolyte imbalance correction

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).[2,†]

*Procedures, diagnoses, or management common in the 6 months preceding a diagnosis of HE. This is not an exhaustive list.

†Per the GRADE System for Evidence: Grade 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; 1=recommendation is "strong," with factors influencing strength of recommendation including the quality of evidence, presumed patient-important outcomes, and costs.[2]

EXAMPLES TO HELP YOU IDENTIFY PATIENTS IN YOUR PRACTICE AT RISK FOR OHE RECURRENCE

Jack, 57 years old, chef

Procedures

- Presenting to GI for variceal surveillance endoscopy
- Band procedure several months ago following variceal hemorrhage

Diagnoses

- History of cirrhosis
- Recently diagnosed with thrombocytopenia
- Has had several OHE episodes in recent months

Management

- Has been on lactulose
- Other medications include proton pump inhibitors, beta blockers, and diuretics

Alice, 60 years old, rideshare driver

Procedures

- Patient with ascites presenting to GI for paracentesis and endoscopy procedures
- Yearly variceal surveillance via endoscopy as well as colonoscopy

Diagnoses

- No indication of variceal hemorrhage but yearly surveillance occurring
- Has a history of HE episodes and is now beginning to present with OHE symptoms

Management

- Currently on a diuretic, beta blockers, and an opioid for chronic pain and has been on and off lactulose therapy

Caregivers can play a critical part in the management of patients with HE[11]

Your patients may not exhibit outward signs of HE at the time of their appointments. Therefore, it is important to ask both patients and their caregivers whether they've experienced (or witnessed) any of the symptoms.

One study found

caregivers identified

25%

of HE episodes[12]

OHE IS A SIGNIFICANT BURDEN ON HEALTHCARE RESOURCES[13]

5.2 days

Average inpatient stay for patients hospitalized for HE in 2020[13,*]

31%

Average readmission rate for HE in 2020[13,*]

*In Medicare patients with diagnosis from HE code group.

OHE is a progressive disease associated with both mental and physical symptoms[2]

Multiple episodes of OHE are associated with persistent deficits in[14]:

- Working memory
- Response inhibition
- Reaction time
- Divided attention

Patient survival rates from time of OHE diagnosis[15]

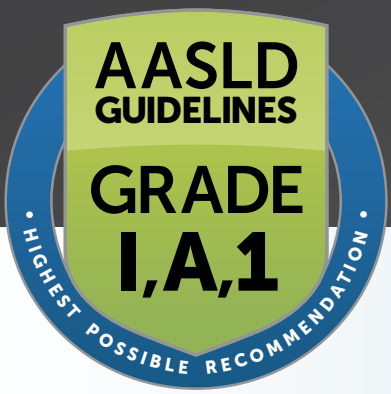
36% 1-year survival rate

15% 5-year survival rate

XIFAXAN WAS GIVEN THE HIGHEST POSSIBLE RECOMMENDATION BY THE AASLD/EASL[2]

Align with the guidelines by using the only FDA-approved agent indicated for the reduction in risk of OHE recurrence in adults[1]

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.[2]



I,A,1 is the highest possible recommendation[2]

GRADE I: Proven in randomized, controlled trials

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

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

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

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.

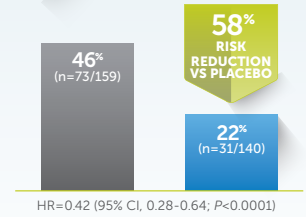
Please see additional Important Safety Information throughout and full Prescribing Information.

XIFAXAN CUT THE RISK OF OHE RECURRENCE AND HE-RELATED HOSPITALIZATIONS IN HALF[1]

Xifaxan® rifaximin 550 mg tablets

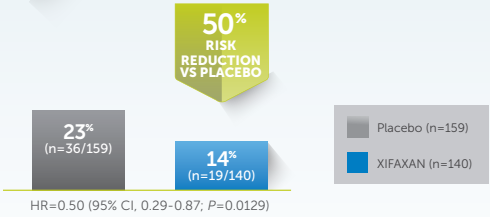
In a clinical trial of adults with OHE

Primary Endpoint — OHE recurrences during 6 months of treatment*



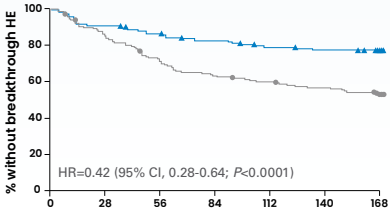
HR=0.42 (95% CI, 0.28-0.64; *P*<0.0001)

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

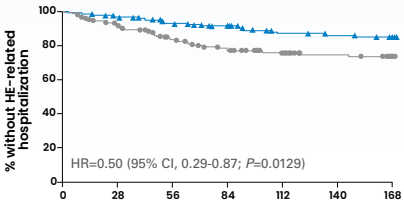


HR=0.50 (95% CI, 0.29-0.87; *P*=0.0129)

Time to first breakthrough HE episode[1]



Time to first HE-related hospitalization[1]



91% of patients in the placebo and XIFAXAN groups were on lactulose[1]

Study design[1,16]

- 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

XIFAXAN number needed to treat (NNT)[16]

Condition	Therapy	To Prevent One	NNT
OHE	XIFAXAN 550 mg + background lactulose†	OHE episode in 6 months	4
		HE-related hospitalization in 6 months	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.[1]

†91% of patients in the XIFAXAN group were on concomitant lactulose.[1]

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.

Please see additional Important Safety Information throughout and full Prescribing Information.

A DEMONSTRATED SAFETY PROFILE[1]

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.

IMPORTANT SAFETY INFORMATION *(continued)*

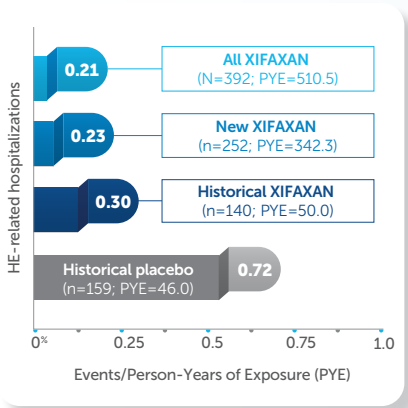
- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential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

THE SAFETY PROFILE OF XIFAXAN WAS EVALUATED FOR 24 MONTHS IN AN OPEN-LABEL EXTENSION (OLE) STUDY[17]

Xifaxan® rifaximin 550 mg tablets

Rates of HE-related hospitalizations (post hoc analysis)[17]



Study design[1,17]

- ≥24-month open-label maintenance (OLM) study of XIFAXAN 550 mg twice daily in patients with HE to assess long-term safety and hospitalization data between the group given placebo in the original randomized controlled trial (RCT) (n=159) and those given XIFAXAN (n=140)
- **Historical XIFAXAN group:** Patients treated with XIFAXAN in the RCT. Patients with Conn scores of 2 were included in the OLM study
- **Historical placebo group:** Patients treated with placebo in the RCT
- **New XIFAXAN group:** New patients treated with XIFAXAN during the OLM study
- **All-XIFAXAN population:** Historical XIFAXAN group and the new XIFAXAN group, 89.8% of whom concomitantly used lactulose
- Concomitant lactulose therapy was optional in the OLM study. Lactulose was used concomitantly by 91% of patients in both arms of the RCT

Safety from ≥24-month open-label study[17]

Adverse events n (rate)	Historical placebo (n=159)	Historical XIFAXAN (n=140)	New XIFAXAN (n=252)	All XIFAXAN (n=392)
Any AE	127 (2.76)	**112 (2.24)**	**236 (0.69)**	**362 (0.71)**
Any serious AE	63 (1.37)	**51 (1.02)**	**158 (0.46)**	**244 (0.48)**
Discontinuations due to AE	45 (0.98)	**30 (0.60)**	**77 (0.22)**	**130 (0.25)**

- Adverse event (AE) rates were calculated as number of patients/PYE, in which PYE=total exposure in days divided by 365.25; PYE reflected the exposure up until the AE occurrence and therefore may have differed from the PYE for the entire patient group[17]
- AEs were comparable to those observed during the 6-month randomized study[17]
- Infections did not increase during the 24-month evaluation[17]
- Six patients (~1%) developed a *C. difficile* infection[17]

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%)

Please see additional Important Safety Information throughout and full Prescribing Information.

ACCURACY MATTERS: CORRECTLY PRESCRIBE XIFAXAN FOR THE REDUCTION IN RISK OF OHE RECURRENCE IN ADULTS[1]

One 550-mg tablet, twice daily—no dose adjustments or titrations needed[1]

- 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**[1]

Can be continued for as long as patient is at risk of recurrent OHE[1]

When prescribing XIFAXAN, use the ICD-10 code for OHE: **K76.82** (Hepatic encephalopathy; indicate lactulose history if applicable)[18,*]

XIFAXAN
550 mg
One tablet twice daily
#60 tablets
for the reduction in risk of OHE recurrence
K76.82*
5 refills

*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.

References: 1. XIFAXAN. Prescribing information. Salix Pharmaceuticals; 2023. Accessed November 3, 2023. https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf **2.** 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 **3.** 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 **4.** Xu J, Murphy SL, Kochanek KD, Arias E. Deaths: final data for 2019. *Natl Vital Stat Rep.* 2021;70(8):1-87. doi:10.15620/cdc:106058 **5.** Chronic liver disease and cirrhosis. Centers for Disease Control and Prevention. Updated January 17, 2023. Accessed August 14, 2023. https://www.cdc.gov/nchs/fastats/liver-disease.htm **6.** Desai AP, Greene M, Nephew LD, et al. Contemporary trends in hospitalizations for comorbid chronic liver disease and substance use disorders. *Clin Transl Gastroenterol.* 2021;12(6):e00372. doi:10.14309/ctg.0000000000000372 **7.** Mansour D, McPherson S. Management of decompensated cirrhosis. *Clin Med (Lond).* 2018;18(suppl 2):s60-s65. doi:10.7861/clinmedicine.18-2-s60 **8.** 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 **9.** Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology.* 2014;59(3):1144-1165. doi:10.1002/hep.26972 **10.** Data on file. IQVIA AI 2022. Salix Pharmaceuticals, Bridgewater, NJ. **11.** Hameed B. A primary care guide to the diagnosis and management of overt hepatic encephalopathy. *Consultant 360.* 2018;58(5):e161. **12.** Landis CS, Ghabril M, Rustgi V, et al. Prospective multicenter observational study of overt hepatic encephalopathy. *Dig Dis Sci.* 2016;61(6):1728-1734. doi:10.1007/s10620-016-4031-7 **13.** Data on file. Forte 2020. Salix Pharmaceuticals, Bridgewater, NJ. **14.** Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology.* 2010;138(7):2332-2340. doi:10.1053/j.gastro.2010.02.015 **15.** Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology.* 2010;51(5):1675-1682. doi:10.1002/hep.23500 **16.** Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071-1081. doi:10.1056/NEJMoa0907893 **17.** Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. *Clin Gastroenterol Hepatol.* 2014;12(8):1390-1397. doi:10.1016/j.cgh.2013.12.021 **18.** ICD-10. Centers for Medicare & Medicaid Services. Updated December 1, 2021. Accessed August 4, 2023. www.cms.gov/Medicare/Coding/ICD10 **19.** Data on file. MMIT September 2023. Salix Pharmaceuticals, Bridgewater, NJ. **20.** Data on file. XIFAXAN CMM Executive Summary 2022. Salix Pharmaceuticals, Bridgewater, NJ. **21.** Help with drug cost. CMS. Accessed August 14, 2023. https://www.medicare.gov/basics/costs/help/drug-costs **22.** Data on file. Patient Copay June 2022 to 2023. Salix Pharmaceuticals, Bridgewater, NJ.

Please see additional Important Safety Information throughout and full Prescribing Information.

XIFAXAN HAS A STRAIGHTFORWARD PRIOR AUTHORIZATION (PA) PROCESS

Xifaxan® rifaximin 550 mg tablets

The XIFAXAN PA process is a simple way to help your adult patients diagnosed with OHE gain access to the treatment you prescribe

When a PA is required, be sure the following information is included and accurate:

- **Indication of OHE: K76.82, the ICD-10 code for OHE (Indicate lactulose history if applicable)[18,*]**
- **Approved dosing for OHE:** #60 XIFAXAN 550-mg tablets, twice daily with refills[1]
- **Age:** 18 years or older[1]
- **Previous therapies tried and failed** (eg, lactulose)

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**.

Help your patients start and stay on XIFAXAN as required

The most common reasons for treatment rejection are failure to initiate a PA, providing inaccurate information, and/or submitting incomplete forms. Watch out for these errors when filling out a PA:

- **Missing signature**
- **Absent or invalid ICD-10 code**
- **Incorrect dosing for the indication**

*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

- 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 full Prescribing Information.

XIFAXAN HAS EXCELLENT INSURANCE COVERAGE[19]

Xifaxan® rifaximin 550 mg tablets

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[20]

98% of commercially insured patients have coverage for XIFAXAN[19,*,†]

100% of Medicare Part D patients have coverage for XIFAXAN[19,*,†]

- Dual-eligibility patients may pay as little as $10.35[21]
  - Some low-income patients may qualify for both Medicare and Medicaid. Direct them to healthcare.gov to determine eligibility

Eligible‡ patients may pay as little as $0 for XIFAXAN

Patients can text "**PAY 0**" to activate

The **XIFAXAN Instant Savings Card** program may provide eligible,‡ commercially insured patients with savings on their monthly copays for XIFAXAN.

- **93% of eligible,‡ commercially insured patients** who had coverage for XIFAXAN **paid $10 or less for their prescription** when a copay card or e-voucher was applied in the last year (June 2022 to June 2023)[22]
- Patients who need assistance with their monthly copays for XIFAXAN can call **1-866-XIFAXAN** (1-866-943-2926)

For more Copay Card details, click here

*Salix Pharmaceuticals does not guarantee coverage or reimbursement for the product.

†Formulary status subject to change.

‡Patient is not eligible if he/she participates in, seeks reimbursement or submits a claim for reimbursement to any federal or state healthcare program with prescription drug coverage, such as Medicaid, Medicare, Medigap, VA, DOD, TRICARE, or any similar federal or state healthcare program (each a Government Program), or where prohibited by law. Patient must be enrolled in, and must seek reimbursement from or submit a claim for reimbursement to, a commercial insurance plan. Offer excludes full-cash–paying patients. Maximum benefits and other restrictions apply. Visit https://xifaxan.copaysavingsprogram.com or call 1-866-XIFAXAN for full eligibility criteria, terms, and conditions.

Please see Important Safety Information throughout and full Prescribing Information.

NOW SHOWING
IBS-D MULTISYMPTOM RELIEF

FOR ADULT PATIENTS WITH IBS-D[1-3]

Short-term therapy

2 weeks of treatment for up to 6 months of relief of abdominal pain and diarrhea[1-3,*]

Median of 10 weeks (range of 6 to 24 weeks).

Patients who experience recurrence can be retreated up to 2 times.

*See TARGET 1, 2, and 3 study data sections.

#1 prescribed medication approved for IBS-D[4,†]

IBS-D, irritable bowel syndrome with diarrhea.

†Based on aggregated total of all prescribers as of June 2023.[4]

INDICATION

XIFAXAN® (rifaximin) 550 mg tablets are indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

IMPORTANT SAFETY INFORMATION

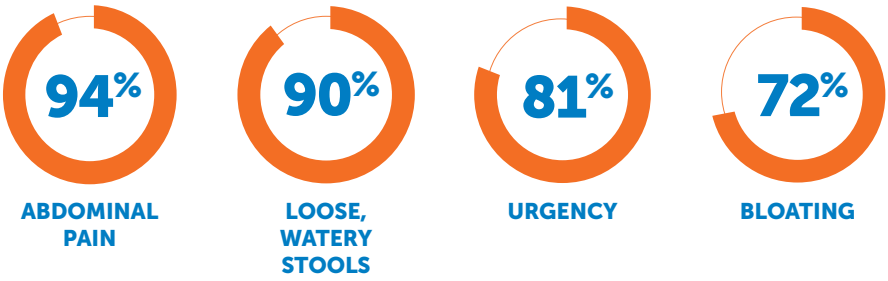
- **XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.**

Please see additional Important Safety Information throughout and full Prescribing Information.

Xifaxan®
rifaximin 550 mg tablets

More than 70% of patients diagnosed with IBS-D experienced multiple symptoms[5,*]

2015 AGA "IBS in America" Online Survey (n=1001): The most common symptoms reported in patients with IBS-D included



Multiple symptoms experienced during the past 12 months*

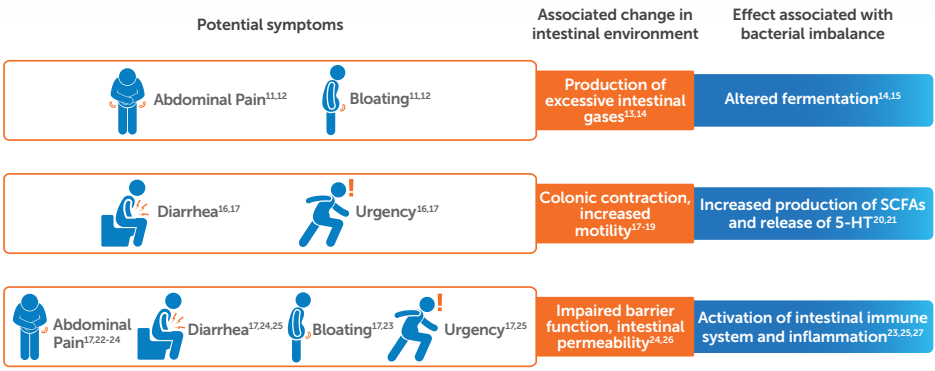
Percentage of patients with IBS-D who responded experiencing these symptoms.

*Data from the "IBS in America" online survey conducted September 14, 2015, through October 29, 2015, for the American Gastroenterological Association (AGA) by GfK Public Affairs & Corporate Communications with financial support from Ironwood Pharmaceuticals, Inc. and Allergan plc. Respondents with an IBS-D diagnosis (n=1001) and respondents with undiagnosed IBS-D (n=586) were asked the following question about a list of symptoms: "Which of the following symptoms have you experienced during the past 12 months?" Data shown reflect the responses of those with an IBS-D diagnosis. These symptoms are not inclusive of all the IBS-D symptoms reported within the survey and treatment was not assessed.

Studies show that many patients with IBS-D have a bacterial imbalance[6-8]

In a US clinical trial, the majority of patients with IBS-D had an abnormal composition of bacteria in the gut[9,*]

Bacterial imbalance has been linked to multiple symptoms of IBS-D[2,6,10]



Additional studies are needed to further clarify the role of gut microbiota in IBS.

XIFAXAN is believed to affect an underlying factor of IBS-D by directly attacking bacteria in the gut that may be linked to IBS-D symptoms[1,6,9,28-30]

- Blocks one of the steps in the transcription of bacterial DNA to RNA
- Inhibits bacterial protein synthesis
- Inhibits bacterial growth

Mechanism of action is unknown and does not imply clinical efficacy

XIFAXAN is the only FDA-approved, nonsystemic IBS-D treatment that alters the microbiome[1,9]

- **Less than 0.4% is absorbed from the GI tract**
- **There is an increased systemic exposure in patients with severe hepatic impairment; caution should be exercised when administering XIFAXAN to these patients**

5-HT, serotonin; SCFA, short-chain fatty acids.

*Data from 93 patients with IBS-D in a prospective TARGET 3 substudy that used lactulose breath testing to predict response to XIFAXAN.[9]

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 full Prescribing Information.

XIFAXAN
STRONG RECOMMENDATION
2020 ACG Guidelines

XIFAXAN was given a strong recommendation* to treat global IBS-D symptoms in the 2020 American College of Gastroenterology (ACG) Clinical Guideline on Managing IBS[31,†]

†Based on a moderate quality of evidence.‡

*Strength of recommendation: Strong=Most patients should receive the recommended course of action. Conditional=Many patients should have this recommended course of action, but different choices may be appropriate for some patients.

†Summary of quality of evidence: High=The estimate of effect is unlikely to change with new data. Moderate=The estimate of effect is uncertain.

Questions and statements used to provide recommendations were based on response to global IBS-D symptoms.

IMPORTANT SAFETY INFORMATION ***(continued)***

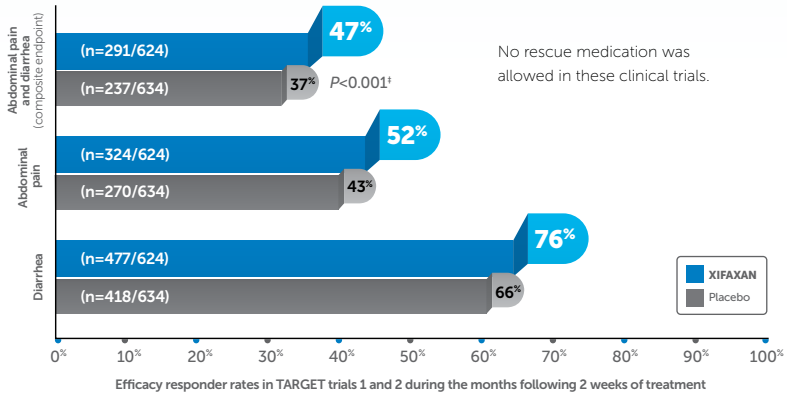
- There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering XIFAXAN to these patients.

Please see additional Important Safety Information throughout and full Prescribing Information.

In adults with IBS-D

2 weeks of XIFAXAN provided significant relief of abdominal pain and diarrhea[1,2,*]

Percentage of composite efficacy responders[†] in TARGET 1 and 2 during the months following 2 weeks of treatment (pooled analysis)



Efficacy responder rates in TARGET trials 1 and 2 during the months following 2 weeks of treatment

TARGET 1 and 2 study design

Two identical phase 3, randomized, double-blind, placebo-controlled trials were conducted over a 3-month period. A total of 1258 patients meeting Rome II criteria for IBS-D were to receive XIFAXAN 550 mg 3 times a day (n=624) or placebo (n=634) for 14 days.

Primary endpoint: Adequate relief of IBS-D signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment, with adequate relief defined as a response of "yes" to the weekly Subject Global Assessment (SGA) question: "In regards to your IBS-D symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS-D symptoms? [Yes/No]."

Primary endpoint results: 41% of patients (254 of 624) in the XIFAXAN 550 mg group, 31% of TARGET 1 placebo group (98 of 314), and 32% of TARGET 2 placebo group (103 of 320) experienced adequate relief of IBS-D signs and symptoms.

Secondary endpoint: In both studies, more patients in the XIFAXAN 550 mg group had adequate relief of global IBS-D symptoms (see primary endpoint for definition) within the first month compared with the placebo group. Relief continued during the first 2 months and throughout all 3 months in both studies. TARGET 1 odds ratio: 1.35 (95% CI: 1.00-1.82). TARGET 2 odds ratio: 1.52 (95% CI: 1.13-2.03).

Composite endpoint: Responder defined by a ≥30% decrease from baseline in abdominal pain, with a weekly mean stool consistency score of <4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment.

*Patients who experience recurrence can be retreated up to 2 times.[1]

[†]Efficacy responder defined as a ≥30% decrease from baseline in abdominal pain, with a weekly mean stool consistency score of <4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment.[1]

[‡]*P*<0.001, represents pooled data.

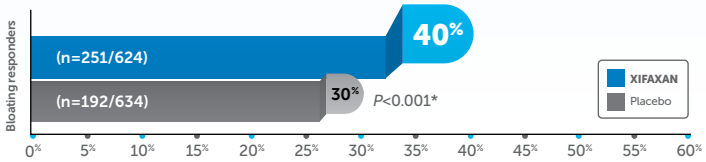
IMPORTANT SAFETY INFORMATION *(continued)*

- 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 full Prescribing Information.

XIFAXAN provided relief of bloating and urgency[2,32]

Percentage of BLOATING responders based on weekly responses in TARGET 1 and 2[2]



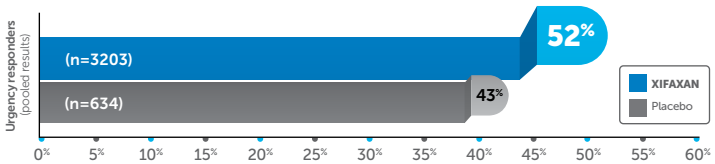
*Represents pooled analysis.

Key secondary endpoint: The proportion of patients who achieved adequate relief of IBS-D–related bloating (ie, responders) for at least 2 of 4 weeks during the month following 14 days of treatment.[2]

A bloating responder was defined as a patient who responded "yes" to the weekly question: "In regards to your IBS-D symptom of bloating, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS-D symptom of bloating? [Yes/No]."[2,†]

†Responses were given during the first 4 weeks of the treatment-free period following 2 weeks of active treatment (primary evaluation period).[2]

Percentage of URGENCY responders based on weekly responses in TARGET 1, 2, and 3 in a pooled post hoc analysis[33]



Secondary endpoint: Change from baseline to each week during the 12-week study duration for sense of urgency.[34,35]

An urgency responder was defined as a patient with a ≥30% decrease from baseline in the percentage of days with urgency for at least 2 of 4 weeks during the month following 14 days of treatment. Urgency was determined based on patient response of "yes" to the daily question: "Have you felt or experienced a sense of urgency today? [Yes/No]."[33]

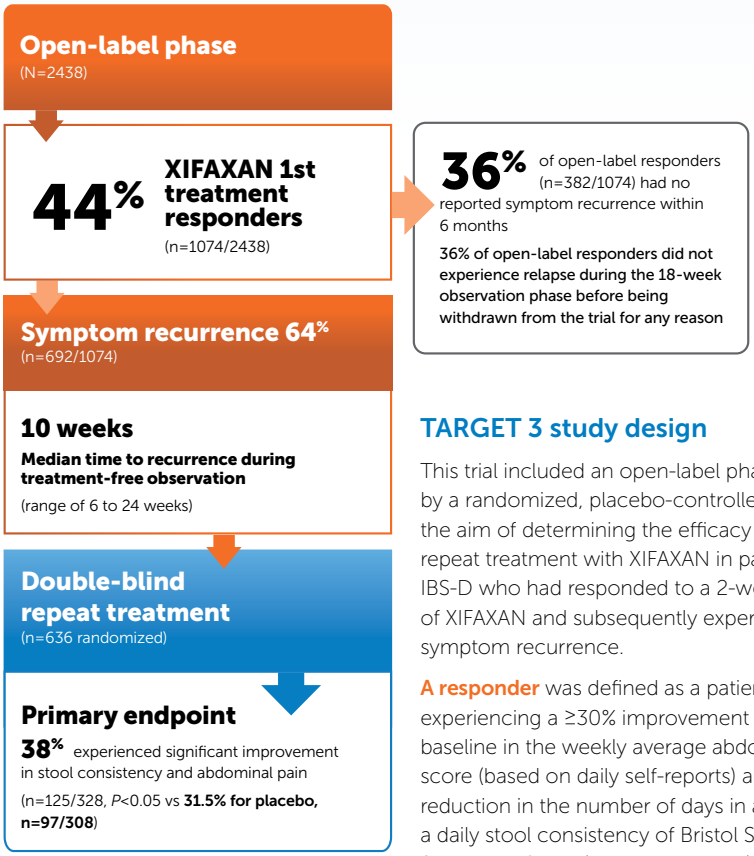
Stool frequency (number of bowel movements per day) was assessed as a secondary endpoint, but there was no meaningful difference between XIFAXAN and placebo.[34,35]

IMPORTANT SAFETY INFORMATION *(continued)*

- In clinical studies, the most common adverse reactions for XIFAXAN in IBS-D (≥2%) were nausea (3%) and ALT increased (2%).
- 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 full Prescribing Information.

Efficacy and safety evaluation of TARGET 3: an extended retreatment trial[1,3]



TARGET 3 study design

This trial included an open-label phase followed by a randomized, placebo-controlled phase, with the aim of determining the efficacy and safety of repeat treatment with XIFAXAN in patients with IBS-D who had responded to a 2-week course of XIFAXAN and subsequently experienced IBS-D symptom recurrence.

A responder was defined as a patient experiencing a ≥30% improvement from baseline in the weekly average abdominal pain score (based on daily self-reports) and a ≥50% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Form Scale type 6 or 7 (mushy or watery) for ≥2 of the 4 weeks after treatment.

Recurrence was defined as the return of abdominal pain or lack of stool consistency for 3 weeks of a rolling 4-week period.

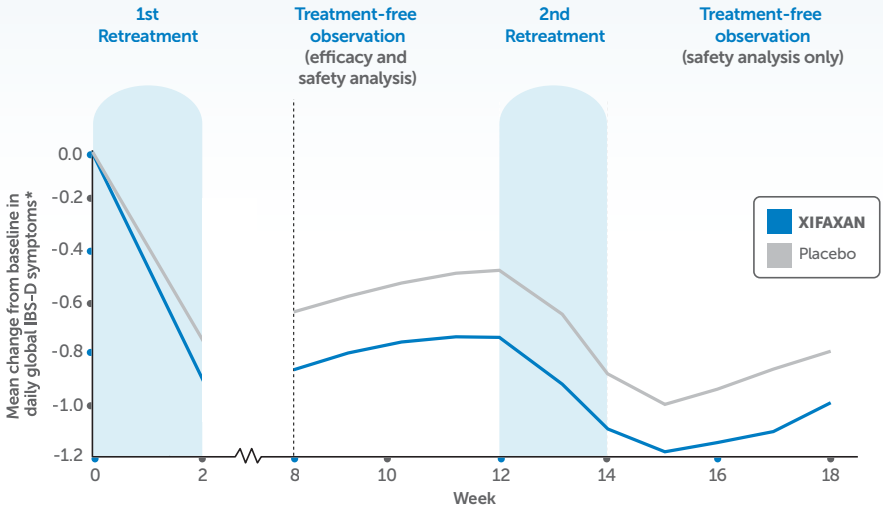
Primary endpoint: The proportion of patients who were responders to repeat treatment in both IBS-D–related abdominal pain and stool consistency during the 4 weeks following the first repeat treatment course.

IMPORTANT SAFETY INFORMATION *(continued)*

- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

Please see additional Important Safety Information throughout and full Prescribing Information.

With repeated treatment, recurring symptoms were less severe than baseline[1,3,*]



Change from baseline in mean daily global IBS-D symptom score during the first and second repeat treatment double-blind phases. Global daily IBS-D symptom score is based on a 6-question patient assessment related to bowel movements, urgency, abdominal pain, bloating, and severity of symptoms. All patients in the XIFAXAN arm of this study were given second retreatment/third treatment regardless of symptom recurrence status.[3]

*Baseline defined as study entry into open-label phase.[3]

In adults with IBS-D

XIFAXAN has a well-established safety profile[1]

Side effects at rates similar to placebo

	TARGET 1 and 2		TARGET 3	
Adverse event	XIFAXAN (n=624)	Placebo (n=634)	XIFAXAN (n=328)	Placebo (n=308)
Nausea	3%	2%	2%	1%
ALT increased†	NA	NA	2%	1%

- Constipation was observed in 0.3%-0.6% of patients treated with XIFAXAN[3,36]
- Did not cause any clinically relevant antibiotic resistance after 1 to 3 treatment cycles[37]

ALT, alanine aminotransferase; NA, not available.

†Most of the events of ALT increase were due to transient increases that resolved over time and were not temporally associated with study drug treatment.[3]

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 full Prescribing Information.

2 weeks of XIFAXAN delivered lasting relief of multiple symptoms[1-3]

Most treatments manage symptoms with continuous daily therapy, but XIFAXAN is different[1,38,39]

One 550-mg tablet 3 times a day with or without food[1]

2 weeks of treatment, not continuous, daily prescription medication[1]

Patients who complete initial treatment can be **retreated up to 2 times** for recurrence[1]

Provides relief of multiple IBS-D symptoms: abdominal pain, diarrhea, bloating, and urgency[1,2,32,33]

XIFAXAN
550 mg
3 times a day for 14 days
#42 tablets
for adult
patients with IBS-D
ICD-10: K58.0*
Can retreat up to 2 times
℞

* The ICD-10 codes 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)*

- 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 full Prescribing Information.

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Xifaxan® rifaximin 550 mg tablets

THE ONLY FDA-APPROVED AGENT INDICATED FOR THE REDUCTION IN RISK OF OHE RECURRENCE IN ADULTS[1]

Highest possible recommendation in AASLD/EASL guidelines (I,A,1)[2,*]

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.*

In a clinical trial, XIFAXAN cut the risk of OHE recurrence and HE-related hospitalizations in half during 6 months of treatment[1,†]

- **58% reduction** in the risk of OHE recurrence (46% for placebo vs 22% for XIFAXAN; HR=0.42 [95% CI, 0.28-0.64; *P*<0.0001])[†]
- **50% reduction** in the risk of HE-related hospitalizations (23% for placebo vs 14% for XIFAXAN; HR=0.50 [95% CI, 0.29-0.87; *P*=0.0129])[†]

Demonstrated safety profile[1]

The most common adverse reactions (occurring in ≥10%) reported by patients in clinical trials using XIFAXAN alone or in combination with lactulose were 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.

XIFAXAN has excellent insurance coverage[19]

- **98%** of commercially insured patients have coverage for XIFAXAN[19,‡,§]
- **100%** of Medicare Part D patients have coverage for XIFAXAN[19,‡,§]
- **93% of eligible,¶ commercially insured patients** who had coverage for XIFAXAN **paid $10 or less for their prescription** when a copay card or e-voucher was applied in the last year (June 2022 to June 2023)[22]

*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]

†See study design on page 7.

‡Salix Pharmaceuticals does not guarantee coverage or reimbursement for the product.

§Formulary status subject to change.

¶See eligibility criteria on page 12.

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.

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 full Prescribing Information.

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