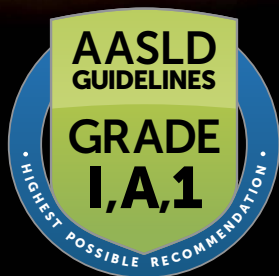


REDUCE THE REPEAT

Disrupt the pattern of overt hepatic encephalopathy (OHE) episodes with XIFAXAN¹



Actor portrayals



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 [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.²

Xifaxan
rifaximin 550 mg tablets

COMMON DRIVERS OF CHRONIC LIVER DISEASE (CLD) AND CIRRHOSIS ARE DIVERSE³⁻⁵

Primary care providers (PCPs) have the opportunity to screen for and identify CLD/decompensated cirrhosis

Driver^{3,4,6}

- Chronic alcohol use
- Hepatitis infections
- Metabolic dysfunction-associated steatotic liver disease (MASLD)
- Metabolic dysfunction-associated steatohepatitis (MASH), an advanced form of MASLD

Comorbidity^{7,8}

- Diabetes
- Heart disease
- Chronic kidney disease

Opportunity

While many patients may see specialists, there is an opportunity to screen for and identify CLD/decompensated cirrhosis because patients may visit PCPs for:

- Chronic disease management
- Altered sleep patterns including somnolence and lethargy/apathy
- Changes in mental status, including disorientation, confusion, and altered attention span
- Mood changes such as euphoria or anxiety
- Changes in overall behavior noticed by their caregivers
- Posthospitalization guidance after OHE episodes

Diabetes/cerebrovascular disease (stroke)

CLD and cirrhosis had **greater mortality in patients aged 25 to 54** than diabetes or cerebrovascular disease (2019)⁹



CLD and cirrhosis were the **10th leading cause of death** in the US in 2022¹⁰



45% increase in total number of CLD-related hospitalizations from 2005 to 2017^{11,*}

*Rates per 1000 persons.

Patients with CLD/decompensated cirrhosis who have portal hypertension have a higher risk of complications, such as^{12,13:}



Varices



Ascites



Hepatic encephalopathy (HE)

MANAGING HE STARTS WITH TIMELY IDENTIFICATION

HE is a brain dysfunction caused by advanced liver disease and/or portosystemic shunting^{2,14,15}

The pathophysiology of HE is complex and involves multiple factors. In patients with decreased hepatic function as a result of cirrhosis, toxins from the gut and gut bacteria (such as ammonia) can enter the bloodstream and reach the brain, where they affect neurotransmission. Episodes of HE may also be brought on by precipitating events, including GI bleeds and infections. These episodes may present as alterations in consciousness, cognition, and behavior that range from minimal to severe.^{2,14,15}

**HE is a primary
complication of cirrhosis²**

UP TO 80%

**of patients with cirrhosis
will eventually develop
some form of HE²**

The guidelines for portal hypertension and cirrhosis call for consideration of the totality of decompensation symptoms when evaluating cirrhosis and setting goals of therapy¹³

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 variceal 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.¹³**

PATIENTS WITH OHE ARE HIDING IN PLAIN SIGHT²

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

MINIMAL

- No outward signs; deficits in psychometric or neuropsychological tests

GRADE 1

- Lack of awareness
- Euphoria or anxiety
- Short attention span
- Inability to add or subtract
- Altered sleep

GRADE 2

- Lethargy/apathy
- No sense of time
- Personality change
- Inappropriate behavior
- Dyspraxia
- Asterixis

GRADE 3

- Somnolence to semistupor
- Responsiveness to stimuli
- Confusion
- Disorientation
- Bizarre behavior

GRADE 4

- Coma

30% TO 40%

of patients with cirrhosis
will develop OHE²

OHE is a progressive disease associated with both mental and physical symptoms²

Multiple episodes of OHE are associated with persistent deficits in¹⁶:

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



Considerations when evaluating a patient for HE^{2,13,17,18,*}



Procedures

- Complete metabolic panels
 - Thrombocytopenia
 - Ammonia surveillance, in combination with other factors
- Screening for changes in mental/physical status and motor function in patients with CLD



Diagnoses

- Identification of decompensated hepatic failure
 - Ascites
 - Variceal hemorrhage
 - Previous HE occurrence
- Alcohol-related disorder
- Primary hypertension
- Referral to GI specialist



Management

- Opioids
- Proton pump inhibitor
- 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).^{2,1}

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

¹Per 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

OHE IS A SIGNIFICANT BURDEN ON HEALTHCARE RESOURCES AND IMPACTS PATIENT SURVIVAL^{19,20}



5.2 days

Average inpatient stay for patients hospitalized for HE in 2020^{19,*}

*In Medicare patients with diagnosis from HE code group.

31%

Average hospital readmission rate for HE in 2020^{19,*}

Patients with HE have significantly decreased survival when compared with other cirrhosis complications^{20,†}

Cirrhosis (no complications)

1-year survival: **83%**

5-year survival: **42%**

Cirrhosis (with variceal bleed)

1-year survival: **80%**

5-year survival: **35%**

Cirrhosis (with ascites)

1-year survival: **71%**

5-year survival: **41%**

Cirrhosis with OHE

from time of OHE diagnosis

36% 1-year survival rate

15% 5-year survival rate

†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.¹⁹



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



ANDY is a 64-year-old retiree, living independently in a suburban 55+ community that's about a 20-minute bus ride from his primary care physician. Andy spends his downtime fishing and reading history books.

Presentation

- Presents in his PCP's office for routine follow-up and diabetes management

Medical History

- Diabetes
- Stage 2 heart failure
- Early chronic kidney disease
- High blood pressure
- Decompensated liver disease-portal hypertension
- Diagnosed with OHE 5 months ago

Treatment History

- On empagliflozin to manage his heart disease and diabetes
- Prescribed lactulose following second OHE episode 4 weeks ago

Treatment Goals

- Avoidance of recurrent OHE, especially since he lives alone



CATHERINE is a 55-year-old accountant, living with her husband in an urban area about 30 minutes from her primary care physician. She leads an active lifestyle and loves watching movies in her downtime.

Presentation

- Presents in her PCP's office for follow-up after recent hospitalization

Medical History

- Chronic back pain
- Diagnosed with chronic liver disease 3 years ago
- Diagnosed with portal hypertension 1 year ago
- Diagnosed with OHE grade 3 at her recent hospitalization

Treatment History

- Uses hydrocodone for control of chronic pain
- Was given acute treatment with lactulose at time of OHE diagnosis
- Was told to visit her PCP for follow-up

Treatment Goals

- Maintenance of active lifestyle
- Prevention of recurrent OHE

Hypothetical patients

Caregivers can play a critical role in the management of patients with HE²¹

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

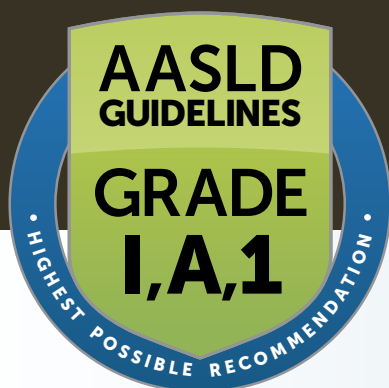
25% of HE episodes²²

XIFAXAN WAS GIVEN THE HIGHEST POSSIBLE RECOMMENDATION BY THE AASLD/EASL²

Xifaxan
rifaximin 550 mg tablets

Align with the guidelines by using the only FDA-approved agent indicated for the reduction in risk of OHE recurrence in adults¹

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 recommendation²

- | | |
|-----------------|---|
| 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 |

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.

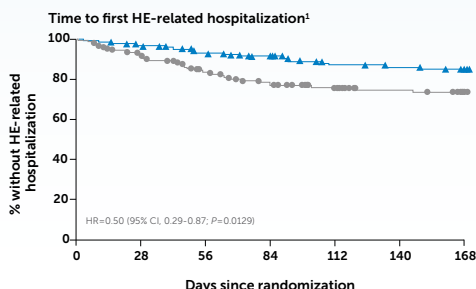
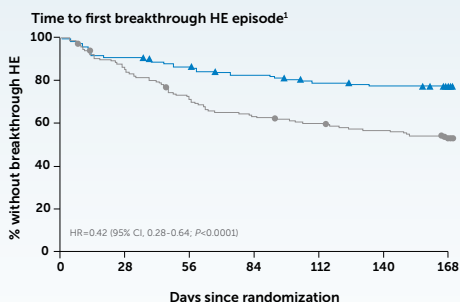
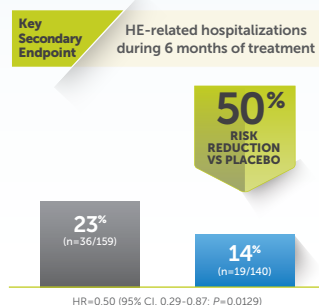
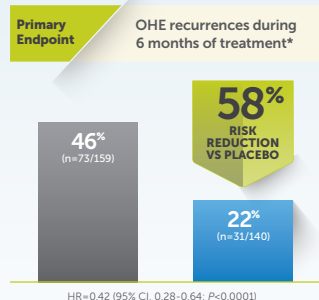
Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.

XIFAXAN CUT THE RISK OF OHE RECURRENCE AND HE-RELATED HOSPITALIZATIONS IN HALF^{1,23}

Xifaxan
rifaximin 550 mg tablets

In a clinical trial of adults with OHE

Efficacy was observed early during treatment



XIFAXAN
(n=140)

Placebo
(n=159)

91% of patients in the placebo and XIFAXAN groups were on lactulose¹

Study design^{1,23}

- 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 asterix grade of 1 each if patient entered study at grade 0
- Key secondary endpoint:** HE-related hospitalization

XIFAXAN number needed to treat (NNT)²³

Condition	Therapy	To Prevent One	NNT
OHE	XIFAXAN 550 mg + background lactulose ¹	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

¹91% 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 [click here](#) for full Prescribing Information.

A DEMONSTRATED SAFETY PROFILE¹

Xifaxan
rifaximin 550 mg tablets

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 above 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 [click here](#) for full Prescribing Information.

ACCURACY MATTERS: CORRECTLY PRESCRIBE XIFAXAN FOR THE REDUCTION IN RISK OF OHE RECURRENCE IN ADULTS¹

Xifaxan
rifaximin 550 mg tablets



One 550-mg tablet, twice daily—no dose adjustments or titrations needed¹

- 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 OHE¹



When prescribing XIFAXAN, use the ICD-10 code for OHE: **K76.82** (Hepatic encephalopathy; indicate lactulose history if applicable)^{24,*}



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

XIFAXAN can be used alone or in combination with lactulose.¹

*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%)

Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.

REAL-WORLD EVIDENCE OF XIFAXAN USE: 30-DAY & ANNUAL REHOSPITALIZATION DUE TO OHE²⁵



Patient classification based on treatment in the 30-day post-discharge window

Initial classification

Received XIFAXAN in 30-day window
with or without delay

XIFAXAN (550 mg BID) treated ($\pm$ lactulose)
N=1452

Did not receive XIFAXAN within 30-day window
after discharge

Not treated with XIFAXAN
N=560

Subclassification

Received XIFAXAN at discharge
without delay
n=1138 (78.4%)

Received XIFAXAN with delay, within
30-day window after discharge
n=314 (21.6%)

Received lactulose alone within
30-day window after discharge
n=337 (60.2%)

No XIFAXAN or lactulose within
30-day window after discharge
n=223 (39.8%)

Sample size and disposition

Commercially insured adults with an initial OHE hospitalization were identified and classified based on treatment received within a 30-day window after discharge and assessed for OHE rehospitalizations and costs.

- OHE patients with ≥ 1 hospitalization* (N=3304)
- Adults 18-64 years old as of initial OHE hospitalization*[†] (N=3162)
- Continuous health plan enrollment[†] (N=2012)

Study design

Claims analysis from MarketScan[®] Commercial Subset (October 1, 2015, through March 31, 2020). Patients were identified and classified based on treatment received in the 30-day post-discharge period. In patients who received XIFAXAN ($\pm$ lactulose) within 30 days (N=1452), 78.4% (n=1138) received treatment at discharge (no delay). In patients who did not receive XIFAXAN within 30 days (N=560), 60.2% (n=337) of patients received lactulose alone.

Inclusion criteria: Adults (18-64 years old) with an initial OHE hospitalization* and continuous health plan enrollment.[†]

Exclusion criteria: Patients who had a liver transplant on or before the discharge date of the first observed OHE hospitalization were excluded from this study.

*Due to the lack of an OHE-specific ICD-10 code at the time of the study period to identify an OHE hospitalization in claims data, medical expert input was used to operationalize the definition of OHE hospitalization.

[†]Also excluding patients who had a liver transplant on or before the discharge date of the first observed OHE hospitalization.

[†]Continuous health plan enrollment ≥ 6 months prior to and ≥ 30 days after the first observed hospitalization.

IMPORTANT SAFETY INFORMATION (continued)

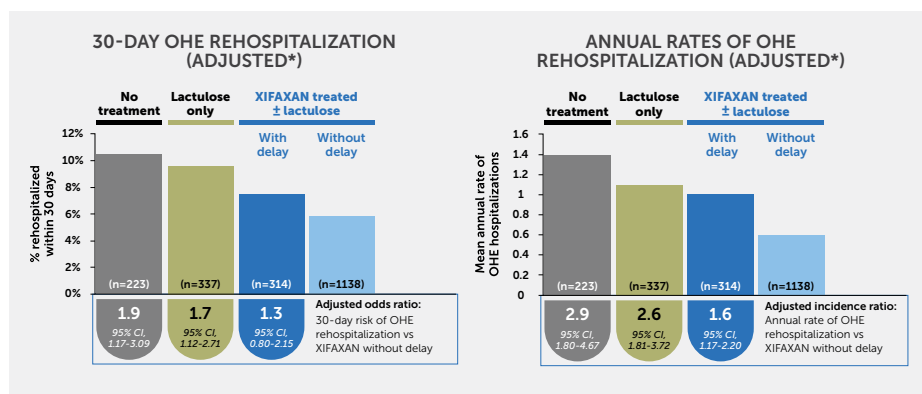
- INR changes have been reported in patients receiving rifaximin and warfarin concomitantly. Monitor INR and prothrombin time. Dose adjustment of warfarin may be required.
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.

OBSERVED REDUCTION IN OHE-RELATED REHOSPITALIZATIONS WITH XIFAXAN²⁵

Xifaxan
rifaximin 550 mg tablets

Compared with patients given XIFAXAN **without delay**, other treatment subgroups showed increased odds of 30-day risk of OHE rehospitalization and increased incidence of annual OHE rehospitalization



Limitations: These results are based on observational claims data and are considered to have relevant limitations. Interpretation of the results is left to the intended audience.

Study limitations

These results are based on observational claims data and are considered to have relevant limitations. Due to the retrospective design of the study, no causality can be established. Claims data from commercially insured populations may not be generalizable to all patients with cirrhosis in the US and can contain omissions in coded procedures, diagnoses, and pharmacy claims. Claims data contain limited clinical and laboratory information; as such, it was not possible to observe inpatient medications nor obtain patients' cirrhosis severity (eg, MELD score, Child-Pugh grades). Despite adjustments for baseline characteristics in OHE hospitalization, residual selection bias and confounding may have remained. Due to the lack of a specific ICD-10 diagnosis code for HE at the time the analyses were conducted, patients with HE were identified using an algorithm developed based on medical expert input. For the purposes of this study, adherence was assumed to have been complete. These real-world evidence study results are based on a retrospective cohort study of claims data with unequal group sizes. This imbalance may potentially affect the generalizability of the findings. The unbalanced number of patients per group may introduce biases.

IR, incidence rate; MELD, Model for End-Stage Liver Disease.

*Analyses were adjusted for a priori selected potential confounding factors associated with OHE hospitalization (ie, age, gender, health plan, region, cirrhosis-specific comorbidity scoring system score, prior gastroenterology consult, duration of index OHE hospitalization, treatment during baseline [eg, rifaximin, HE prophylaxis with antibiotics], indicators of portal hypertension [eg, varices], and factors associated with HE [eg, frailty index]).

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 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:



Dosing for OHE: #60 XIFAXAN 550-mg tablets, twice daily with refills¹

Click here to download the Write It Right flashcard



Accurate indication of OHE: K76.82, the ICD-10 code for OHE (Indicate lactulose history if applicable)^{24,*}



Age: 18 years or older¹



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**.

*See ICD-10 code disclaimer on page 11.

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.

References: 1. XIFAXAN. Prescribing information. Salix Pharmaceuticals; 2023. Accessed November 15, 2024. <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. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology*. 2017;152(5):1090-1099.e1. doi:10.1053/j.gastro.2017.01.003 4. Kim D, Li AA, Gadiparthi C, et al. 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Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.

XIFAXAN HAS EXCELLENT INSURANCE COVERAGE²⁶

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 pharmacies²⁷

98% of commercially insured patients have coverage for XIFAXAN^{28,*†}

100% of Medicare Part D patients have coverage for XIFAXAN^{28,*†}

- Dual-eligibility patients may pay as little as \$10.35²⁹
 - 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.

- **94% 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 (October 2023 to October 2024)³⁰
- 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.

It's time to talk about

IBS-D MULTISYMPTOM RELIEF

for adult patients¹⁻³



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,†}**



Actor portrayals

IBS-D, irritable bowel syndrome with diarrhea.

[†]Based on aggregated total of all prescribers as of August 2024.⁴

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 [click here](#) for full Prescribing Information.

Xifaxan®
rifaximin 550 mg tablets

>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



**ABDOMINAL
PAIN**



**LOOSE,
WATERY
STOOLS**



URGENCY



BLOATING

Multiple symptoms experienced during the past 12 months*

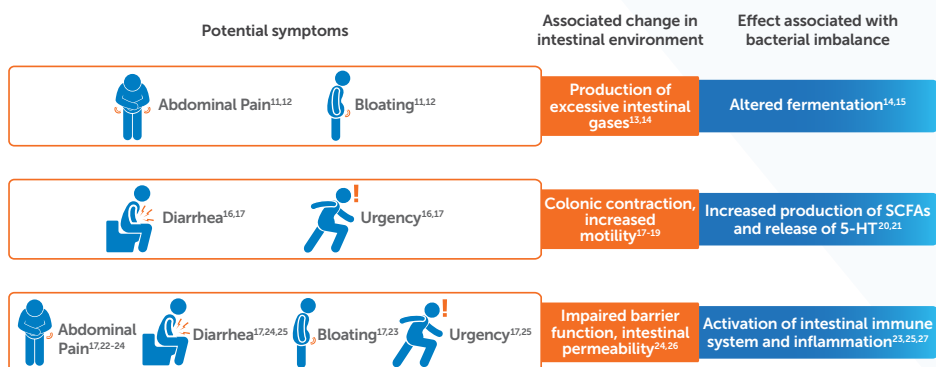
Percentage of patients with IBS-D who responded experiencing these symptoms.

*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 imbalance⁶⁻⁸

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 [click here](#) for full Prescribing Information.



Now is a good time to talk about treatment

XIFAXAN was given a strong recommendation* to treat global IBS-D symptoms³¹

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.³¹

[‡]Summary of quality of evidence: High=The estimate of effect is unlikely to change with new data.
Moderate=The estimate of effect is uncertain.³¹

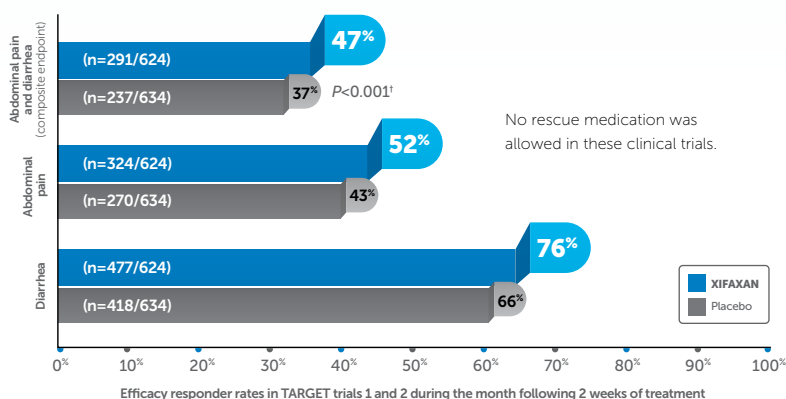
IMPORTANT SAFETY INFORMATION (continued)

- 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 [click here](#) for full Prescribing Information.

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 month following 2 weeks of treatment (pooled analysis)



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 in both studies, 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

¹P<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.

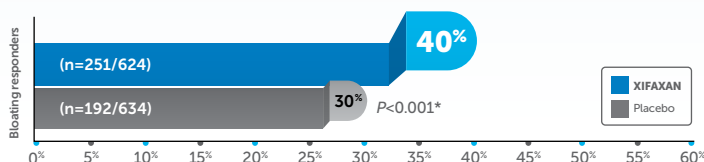
Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.

There's never a bad time to talk about relief

Xifaxan
rifaximin 550 mg tablets

XIFAXAN provided relief of bloating and urgency^{2,32}

Percentage of **BLOATING** responders based on weekly responses in TARGET 1 and 2²



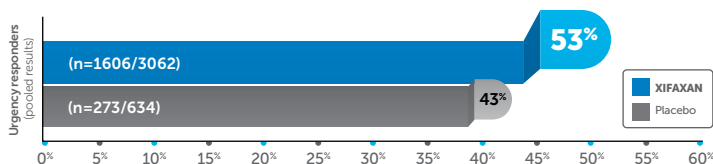
*Represents pooled analysis.

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 analysis³³



Post hoc endpoint: Change from baseline to each week during the 12-week study duration for sense of urgency.³³

An urgency responder was defined as a patient with a $\geq 30\%$ 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].”³⁴

Stool frequency (number of bowel movements per day) was assessed as a secondary endpoint, but there was no meaningful difference between XIFAXAN and placebo.^{35,36}

IMPORTANT SAFETY INFORMATION (continued)

- In clinical studies, the most common adverse reactions for XIFAXAN in IBS-D ($\geq 2\%$) 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 [click here](#) for full Prescribing Information.

Efficacy and safety evaluation of TARGET 3: an extended retreatment trial^{1,3}

Open-label phase (N=2438)

44% **XIFAXAN 1st treatment responders**
(n=1074/2438)

36% of open-label responders (n=382/1074) had no reported symptom recurrence within 6 months

36% of open-label responders did not experience relapse during the 18-week observation phase before being withdrawn from the trial for any reason

Symptom recurrence 64%
(n=692/1074)

10 weeks

Median time to recurrence during treatment-free observation
(range of 6 to 24 weeks)

Double-blind repeat treatment
(n=636 randomized)

Primary endpoint

38% experienced significant improvement in stool consistency and abdominal pain
(n=125/328, $P<0.05$ vs **31.5% for placebo**, n=97/308)

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 $\geq 30\%$ improvement from baseline in the weekly average abdominal pain score (based on daily self-reports) and a $\geq 50\%$ 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)

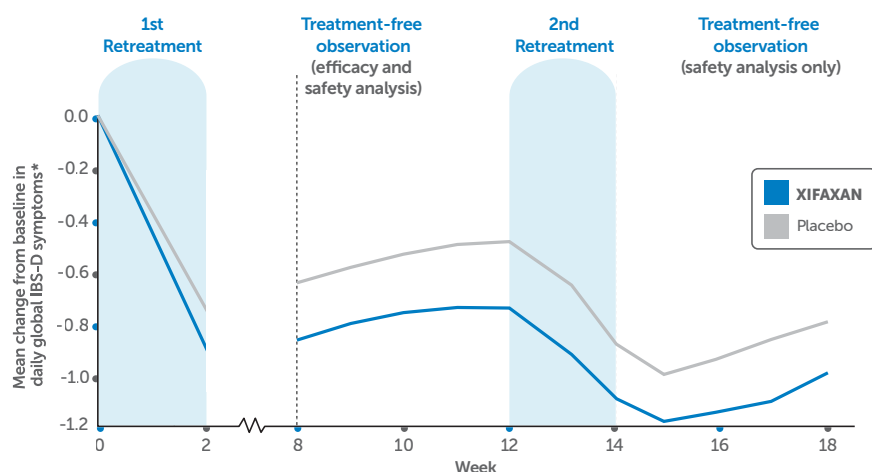
- XIFAXAN may cause fetal harm. Advise pregnant women of the potential risk to a fetus.

Please see additional Important Safety Information throughout and [click here](#) for full Prescribing Information.



Why not explore the route to relief?

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

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 has a well-established safety profile¹

Side effects at rates similar to placebo

Adverse event	TARGET 1 and 2		TARGET 3	
	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^{3,37}
- Did not cause any clinically relevant antibiotic resistance after 1 to 3 treatment cycles³⁸

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 (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.

Dosing XIFAXAN: 2 weeks of treatment delivered lasting relief* of multiple symptoms¹⁻³

Xifaxan
rifaximin 550 mg tablets

Most treatments manage symptoms with continuous daily therapy, but XIFAXAN is different^{1,39,40}



One 550-mg tablet
3 times a day with or
without food¹



2 weeks of treatment,
not continuous, daily
prescription medication¹



Patients who complete
initial treatment can be
retreated up to 2 times
for recurrence¹



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: K58.0¹
Can retreat up to 2 times
R_x

*In studies, more patients taking XIFAXAN vs placebo had IBS-D symptom relief the month following 2 weeks of treatment. Median of 10 weeks (range 6-24 weeks) of abdominal pain and diarrhea relief.^{1,2}

¹The 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.

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



Timely identification of OHE in your patients with decompensated cirrhosis is critical^{2,13,20}

Up to 40% of patients with cirrhosis will develop OHE.



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 profile¹

The most common adverse reactions (occurring in $\geq 10\%$) 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 coverage²⁶

- **98%** of commercially insured patients have coverage for XIFAXAN^{28,‡,§}
- **100%** of Medicare Part D patients have coverage for XIFAXAN^{28,‡,§}
- **94% 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 (October 2023 to October 2024)³⁰

*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 9.

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

[§]Formulary status subject to change.

³⁰See eligibility criteria on page 15.

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 [click here](#) for full Prescribing Information.

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