#1 PRESCRIBED MEDICATION APPROVED FOR IBS-D[1]*

Put your adult patients with IBS-D on

A Short Path to Lasting Relief

Just 2 WEEKS OF TREATMENT provided up to 6 MONTHS OF RELIEF from abdominal pain and diarrhea.[2†]

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

Median of 10 weeks (range of 6 to 24 weeks).[2]

†See TARGET 3 Study Design on Efficacy page.

For multiple IBS-D symptom relief, there's XIFAXAN[2]

IBS-D=irritable bowel syndrome with diarrhea

*Based on aggregated total of all prescribers as of December 2020.

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 accompanying full Prescribing Information.

Xifaxan® rifaximin 550 mg tablets

Make a symptom-based diagnosis with confidence[3]

History based on Rome IV criteria[3,4]

- Abdominal pain at least 1 day per week for the past 3 months* associated with 2 or more of the following:
  - Defecation
  - Change in stool frequency
  - Change in stool form
- **Use the 25% Rule:** <25% hard, lumpy stool and >25% loose, watery stool

Exclusion of alarm features[3,5]

- Symptom onset after age 50
- Severe or worsening symptoms
- Unexplained weight loss
- Nocturnal diarrhea
- Rectal bleeding
- Iron-deficiency anemia
- Family history of colon cancer, celiac disease, IBD

Physical exam and limited diagnostic testing[3]

In diagnosed patients

97.1% accuracy for IBS with symptom-based diagnostic criteria[6†]

IBD=inflammatory bowel disease; IBS=irritable bowel syndrome

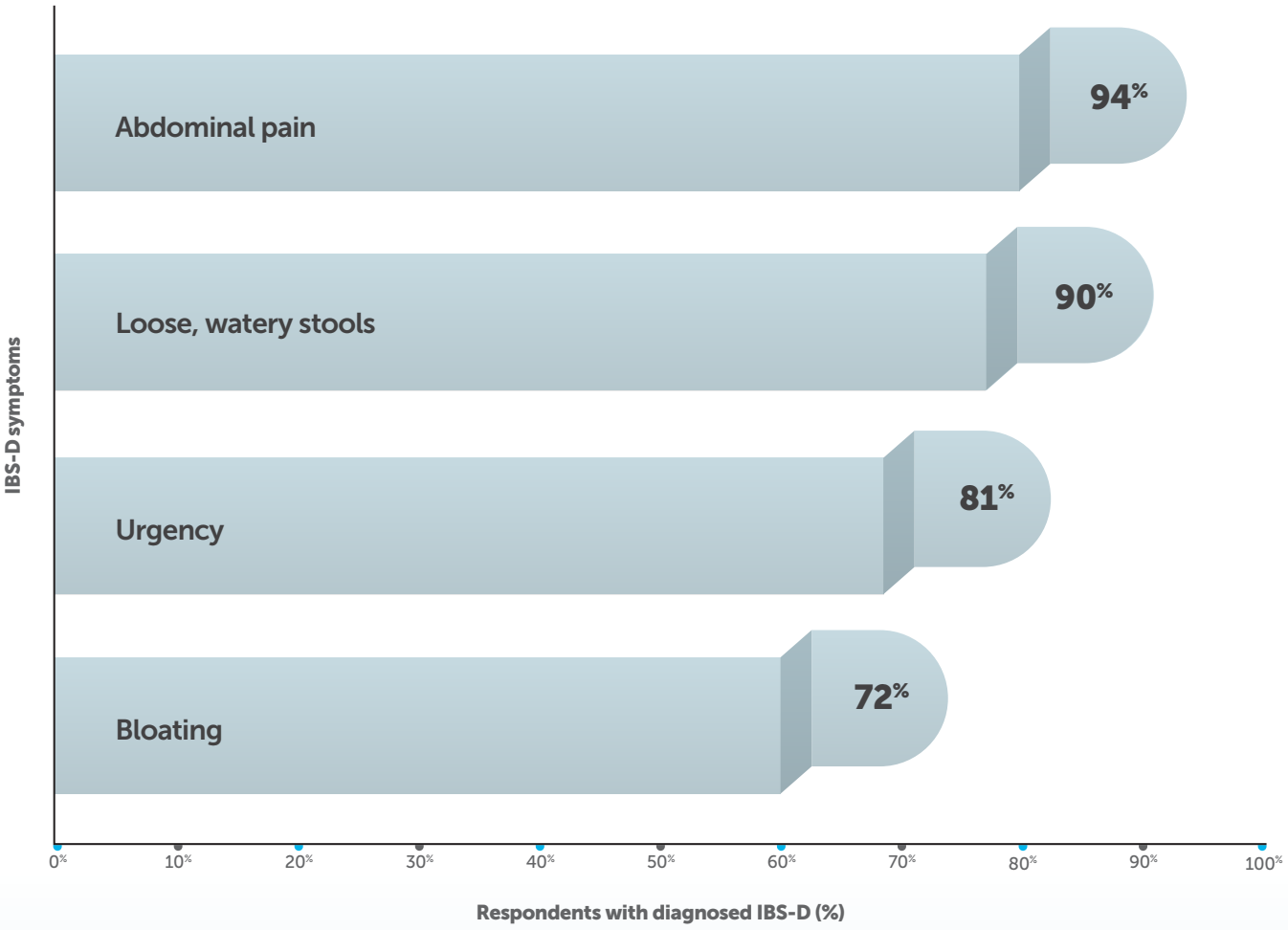
*With symptom onset at least 6 months prior to diagnosis.

†Population sample of 5931 adults using Rome IV Diagnostic Questionnaires.

More than 70% of patients suffered from multiple IBS-D symptoms in a 12-month period[7‡]

According to a 2015 online survey conducted by the American Gastroenterological Association (AGA) that included 1001 respondents with an IBS-D diagnosis

Symptoms experienced during the past 12 months‡



‡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 without a formal IBS-D diagnosis (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.

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

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[3†]

†Based on a moderate quality of evidence[3‡]

*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;
Low; ↓
Very low=Estimate of effect is very uncertain.

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

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 accompanying full Prescribing Information.

Studies show that many IBS-D patients have a bacterial imbalance[9-11]

In a US clinical trial, the majority of IBS-D patients had an abnormal composition of bacteria in the gut[12]

Data from 62/93 patients from a prospective sub-study in TARGET 3.[12]

Bacterial imbalance has been linked to symptoms of IBS-D[9,13,14]

Effect associated with bacterial imbalance	Associated change in intestinal environment	Potential resulting symptoms
Altered fermentation[15,16]	Production of excessive intestinal gases[16,17]	Abdominal pain and bloating[18,19]
Increased production of SCFAs and release of 5-HT[20-22]	Colonic contraction, increased motility[23-25]	Diarrhea and urgency[21,24,26]
Activation of intestinal immune system and inflammation[27-29]	Impaired barrier function, intestinal permeability[30,31]	Abdominal pain, diarrhea, bloating, and urgency[27,28,30-32]

5-HT=serotonin; SCFA=short-chain fatty acids

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[2,9,12,33-36]

- Blocks one of the steps in the transcription of bacterial DNA to RNA[2]
- Inhibits protein synthesis[2]
- Inhibits bacterial growth[2]

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[2]

- **Less than 0.4% is absorbed from the GI tract[2]**
- There is increased systemic exposure in patients with severe hepatic impairment; caution should be exercised when administering XIFAXAN to these patients[2]

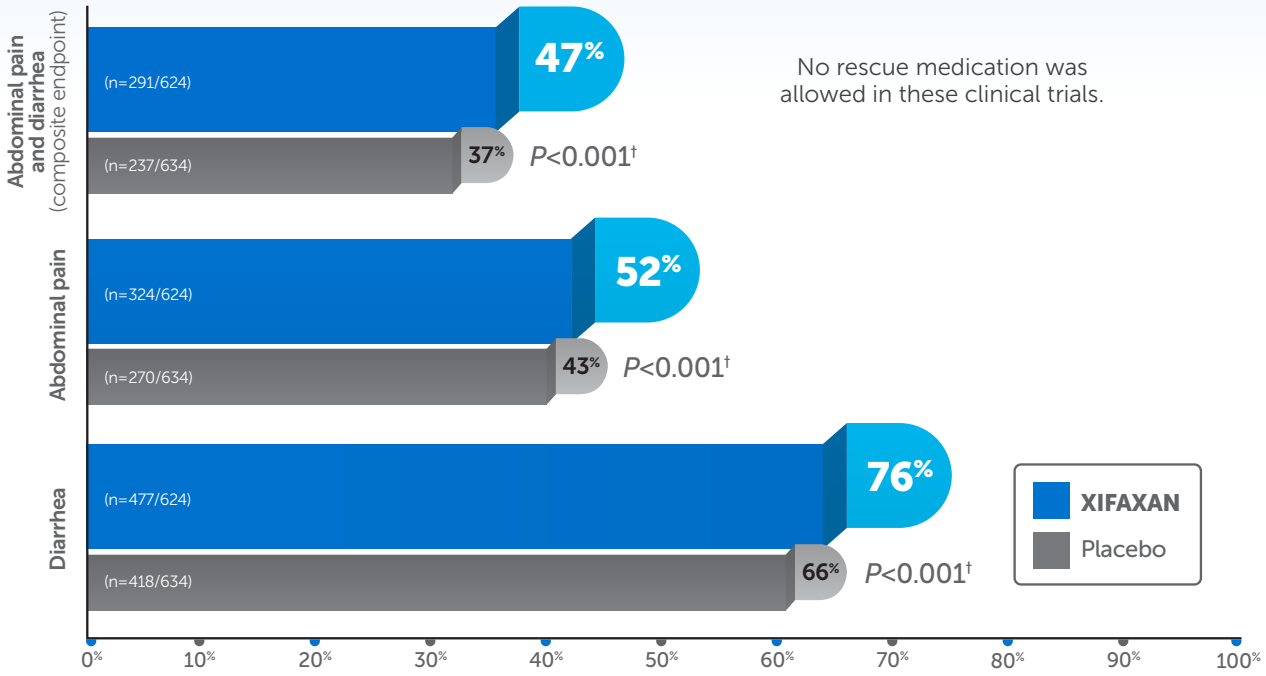
IMPORTANT SAFETY INFORMATION *(continued)*

- 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 accompanying full Prescribing Information.

Just 2 weeks of XIFAXAN provided significant relief from both abdominal pain and diarrhea[2,13*]

In TARGET 1 & 2



No rescue medication was allowed in these clinical trials.

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

†*P*<0.001 represents pooled data.

TARGET 1 and 2 study design[2,13]

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

Primary endpoint: Adequate relief of IBS 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 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 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, *P*=0.01), and 32% of TARGET 2 placebo group (103 of 320, *P*=0.03) experienced adequate relief of IBS signs and symptoms.

Composite endpoint: ≥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.

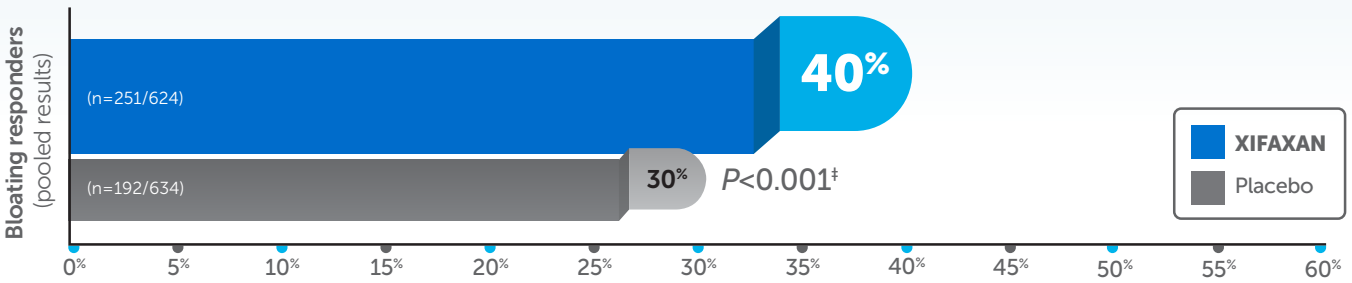
IMPORTANT SAFETY INFORMATION *(continued)*

- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin.

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

XIFAXAN provided significant relief of bloating and urgency[13,37]

Percentage of BLOATING responders based on weekly responses in TARGET 1 & 2[13]



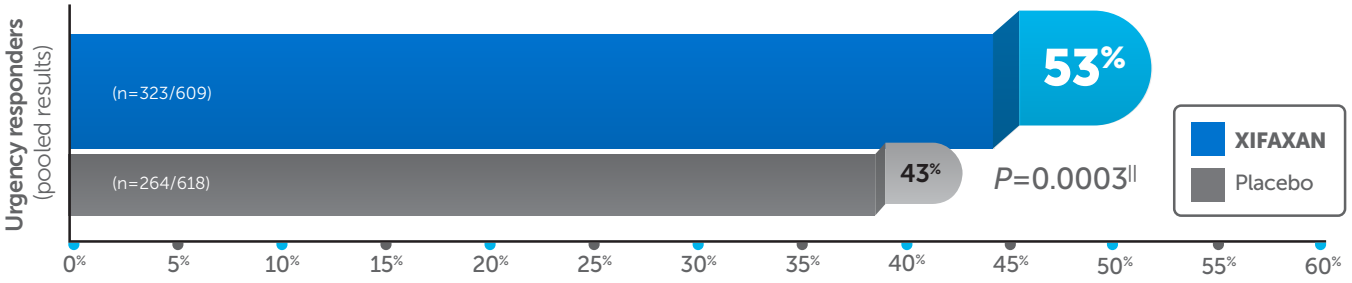
‡*P*<0.001 represents pooled data.

Key secondary endpoint: The proportion of subjects who achieved adequate relief of IBS-related bloating (ie, responders) for at least 2 of 4 weeks during the month following 14 days of treatment.[13]

A bloating responder was defined as a patient who responded "yes" to the weekly question: *"In regards to your IBS 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 symptom of bloating? [Yes/No]."*[13§]

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

Percentage of URGENCY responders based on weekly responses in TARGET 1 & 2 in a pooled post hoc analysis[37]



‖*P*=0.0003 represents data from pooled post hoc analysis.

Stool frequency (number of bowel movements per day) was assessed as a secondary endpoint, but there was no statistically significant difference between XIFAXAN and placebo.[38]

- **Urgency responder:** 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]"*[37]

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%).

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

SHORT-TERM THERAPY[2]

Just 2 weeks of treatment.[2]

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

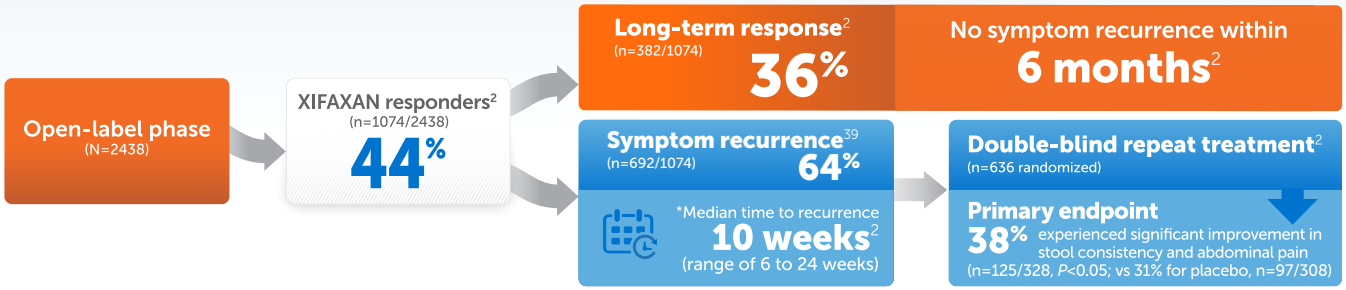
LASTING RELIEF[2]

Up to 6 months of relief.[2]

Median of 10 weeks (range of 6 to 24 weeks).[2]

In TARGET 3 (retreatment study)

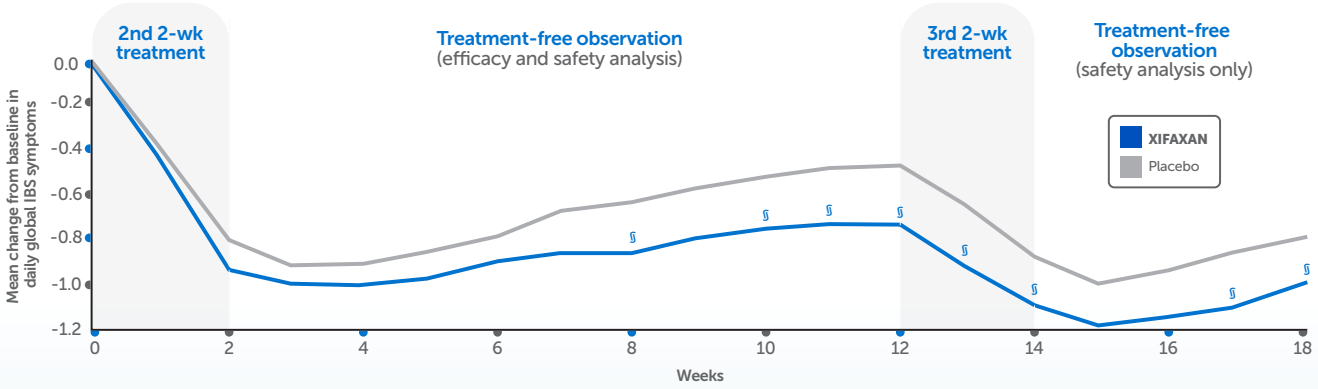
Just 2 weeks of treatment provided significant relief for up to 6 months from abdominal pain and diarrhea[2*†]



TARGET 3 study design[2,39]

- The primary focus was to assess response to treatment during an 18-week observation phase after initial 4-week follow-up (total of 22 weeks following 2-week treatment). If a patient responded to open-label treatment but later experienced a recurrence, they entered the randomized, double-blind retreatment phase. Randomized patients then received a repeat treatment with either XIFAXAN or placebo
- **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 Scale type 6 or 7 (mushy or watery) for ≥2 weeks during the month following 2 weeks of 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** in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain and stool consistency
- [†]Patients who experience recurrence can be retreated up to 2 times

After initial relief, recurring symptoms were less severe than baseline[2,39‡]



Change from baseline in mean daily global IBS 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, 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.

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

[§]Statistically significant difference vs placebo (least squares mean data). Data were analyzed using last observation carried forward methodology.

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%).

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

In adults with IBS-D

Well-established safety profile[2]

Side effects at rates similar to placebo[2]

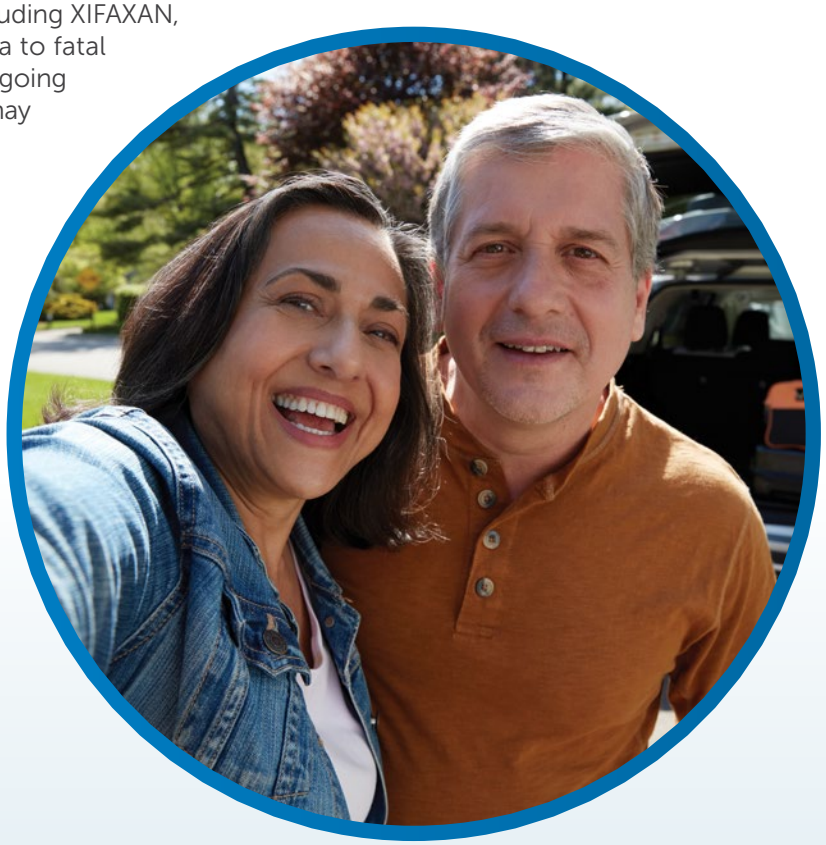
	TARGET 1 & 2		TARGET 3	
Adverse event	XIFAXAN (n=624)	Placebo (n=634)	XIFAXAN (n=328)	Placebo (n=308)
Nausea	3%	2%	2%	1%
ALT increased[¶]	NA	NA	2%	1%

- Constipation was observed in only 0.5% of XIFAXAN patients[38]
- Did not cause any clinically relevant antibiotic resistance after 1 to 3 treatment cycles[40]

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.
- 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 accompanying full Prescribing Information.



ALT=alanine aminotransferase

NA=not available

‖Based on aggregated total of all prescribers as of December 2020.

¶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.

Just 2 weeks of treatment

Most treatments only manage symptoms with continuous therapy, but XIFAXAN is different[2,41,42]

- **Just 2 weeks of treatment,** not continuous daily prescription medication[2]
- **One 550 mg tablet** 3 times a day with or without food[2]
- Patients who experience recurrence can be **retreated up to 2 times**[2]

ICD-10 code for IBS-D[43†]	
K58.0	Irritable bowel syndrome with diarrhea

XIFAXAN was given a strong recommendation[‡] to treat global IBS-D symptoms in the 2020 ACG Clinical Guideline on Managing IBS[39§]

[§]Based on a moderate quality of evidence[31‖]

[‡]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;
Low;
Very low=Estimate of effect is very uncertain.

Think XIFAXAN for multiple IBS-D symptom relief

- **Provided relief of multiple IBS-D symptoms: abdominal pain, diarrhea, bloating, and urgency**[2,13,37]
- No contraindications to many concomitant conditions of IBS-D, including psychiatric disorders[2]
- No observed anticholinergic reactions (eg, dry mouth, blurred vision, urinary incontinence) in clinical trials[2]
- No titration required[2]
- Nonsystemic treatment[2]

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

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

*Based on aggregated total of all prescribers as of December 2020.

†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.

SHORT-TERM THERAPY[2]

Just 2 weeks of treatment.[2]

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

LASTING RELIEF[2]

Up to 6 months of relief.[2]

Median of 10 weeks (range of 6 to 24 weeks).[2]

XIFAXAN has excellent insurance coverage[38]

98% of commercially insured patients have coverage for XIFAXAN[38¶#]

- 70% of these patients have access to XIFAXAN without step therapy[38]

96% of Medicare patients have coverage for XIFAXAN[38¶#]

Easy prior authorization (PA) process when needed

Remember to:

A **Age:** Patients must be 18 years or older

D **Diagnosis of IBS-D:** ICD-10 code is K58.0[43#]

D **Dosing for IBS-D:** XIFAXAN 550 mg 3 times a day for 2 weeks; #42 tablets[2]

Document any and all prescriptions (eg, antispasmodics and antidiarrheals) or over-the-counter medications that the patient has tried and failed for step edits.

covermymeds®: A resource for your prior authorizations

79% PA approval rate in 2020 for XIFAXAN for IBS-D when submitted through CoverMyMeds[38]

To start a PA for XIFAXAN, you can go to **covermymeds.com** or call **1-866-452-5017**.

Being proactive with PAs leads to higher approval rates.[38]

¶Formulary status subject to change.
#See ICD-10 code disclaimer on Dosing page.

IMPORTANT SAFETY INFORMATION *(continued)*

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

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

Xifaxan® F1RST
rifaximin 550 mg tablets

#1 PRESCRIBED MEDICATION APPROVED FOR IBS-D[1]*

Help your eligible† patients save on XIFAXAN

XIFAXAN Instant Savings Card program may help eligible†, commercially insured patients with coverage for XIFAXAN **pay as little as $0**

Patients who need assistance with their monthly copays can **call 1-866-XIFAXAN (1-866-943-2926)**

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

90% of eligible†, commercially insured patients who had coverage for XIFAXAN

PAID $10 OR LESS for their prescription when a copay card or eVoucher was applied in 2020[38]

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 accompanying full Prescribing Information.

*Based on aggregated total of all prescribers as of December 2020.

†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.

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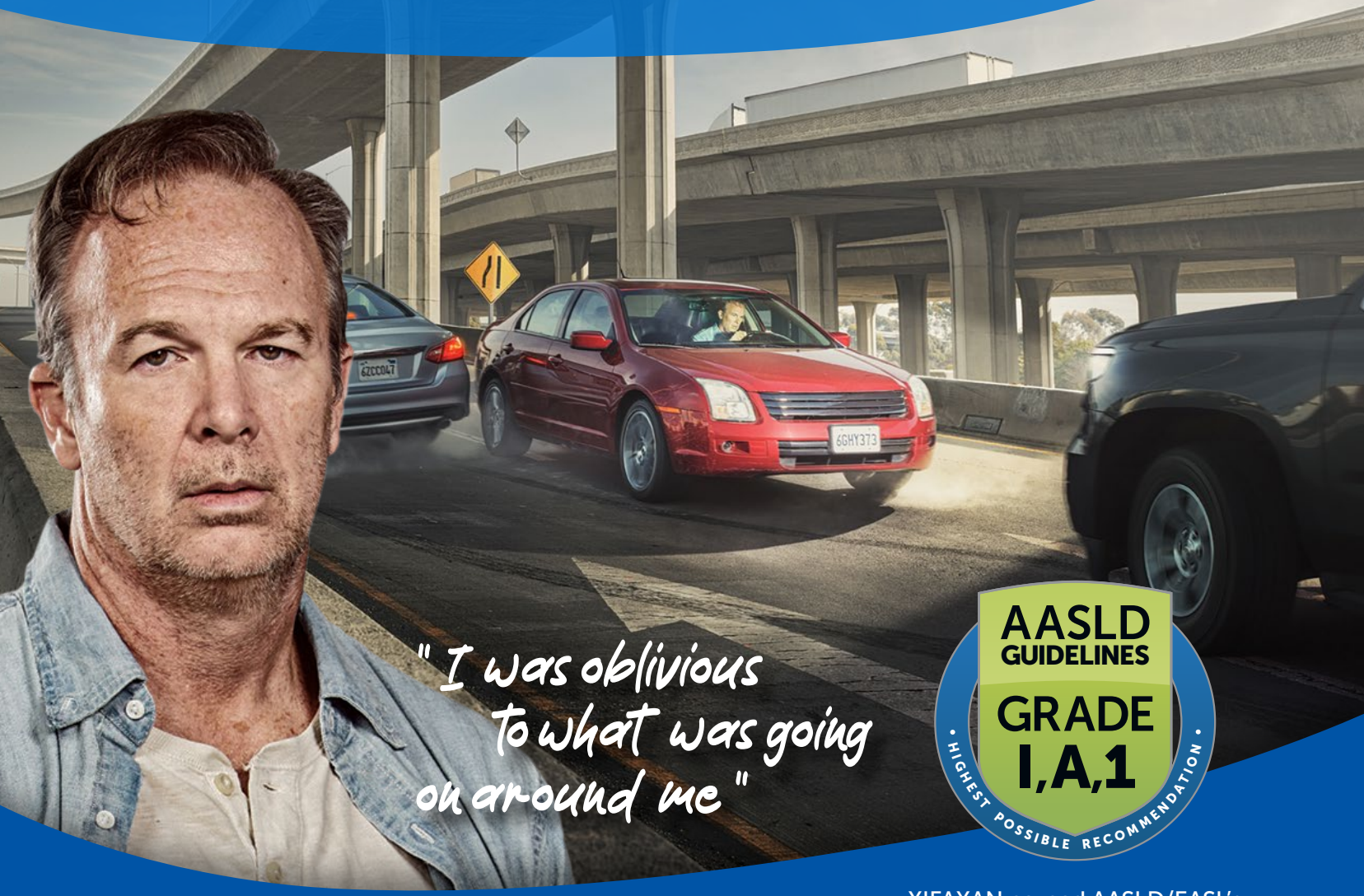
Bridgewater, NJ. **39.** Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology.* 2016;151(6):1113-1121. **40.** Pimentel M, Cash BD, Lembo A, Wolf RA, Israel RJ, Schoenfeld P. Repeat rifaximin for irritable bowel syndrome: no clinically significant changes in stool microbial antibiotic sensitivity. *Dig Dis Sci.* 2017;62(9):2455-2463. **41.** Viberzi [prescribing information]. Madison, NJ: Allergan. **42.** Amitriptyline HCl [prescribing information]. Princeton, NJ: Sandoz. **43.** ICD-10. Centers for Medicare & Medicaid Services. www.cms.gov/Medicare/Coding/ICD10. Accessed August 7, 2020.

Another episode of overt hepatic encephalopathy (OHE) may be right around the corner.

What can you do to reduce your patients' risk of recurrence?



AASLD GUIDELINES
GRADE I,A,1
HIGHEST POSSIBLE RECOMMENDATION

XIFAXAN earned AASLD/EASL's highest possible recommendation (GRADE I,A,1) as an add-on therapy to lactulose to reduce the risk of overt HE recurrence after a patient has a recurrence while on lactulose alone.[1]

Help reduce their risk with XIFAXAN[2]

Xifaxan® rifaximin 550 mg tablets

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 accompanying full Prescribing Information.

Cirrhosis is a severe form of chronic liver disease that puts ~630,000 Americans in danger of severe consequences[3]

Common drivers of chronic liver disease (CLD) and cirrhosis are diverse[4,5]:

- Chronic alcohol use
- Hepatitis infections
- Nonalcoholic steatohepatitis (NASH)
- Nonalcoholic fatty liver disease (NAFLD)

Mortality in these patients is high[6]

11TH
LEADING CAUSE

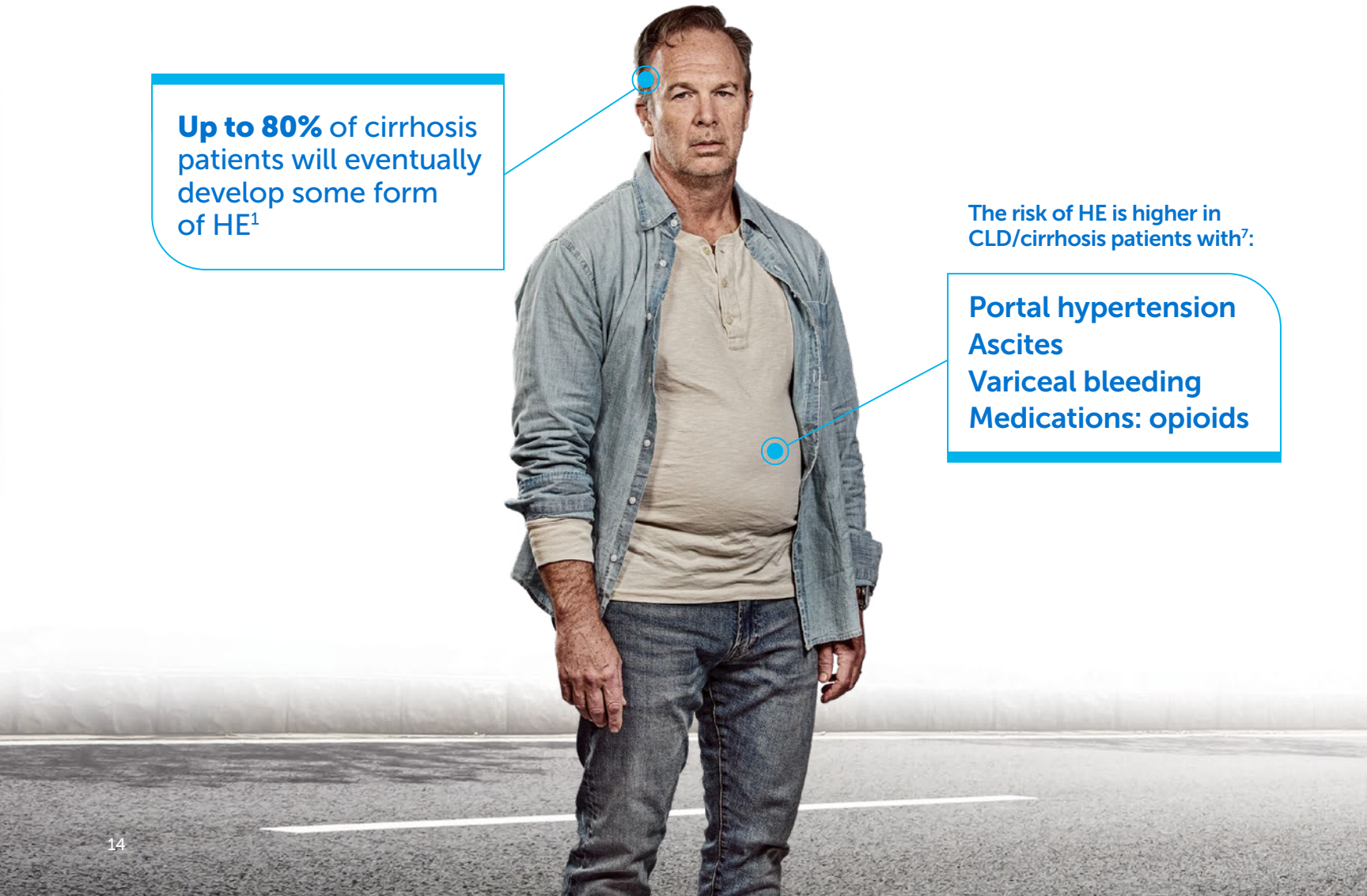
CLD and cirrhosis are the **11th leading cause of death** in the US[6]

DIABETES/ STROKE

CLD and cirrhosis have **greater mortality in patients aged 25 to 54** than diabetes or stroke[6]

HE is a primary complication of cirrhosis

Up to 80% of cirrhosis patients will eventually develop some form of HE[1]



The risk of HE is higher in CLD/cirrhosis patients with[7]:

Portal hypertension
Ascites
Variceal bleeding
Medications: opioids

OHE is a high driver of hospitalizations and readmissions[8,9]

225%

Increase in OHE-related hospitalizations from 2005-2014[8]*

7.1 days

Average inpatient stay for patients hospitalized for HE in 2016[9]

53%

Average 30-day readmission rate for HE in 2016[9]

*ICD-9-CM codes at hospital discharge: 291.2 (alcohol-induced persisting dementia), 348.3 (encephalopathy, unspecified), and 572.2 (hepatic encephalopathy); all listed diagnoses.

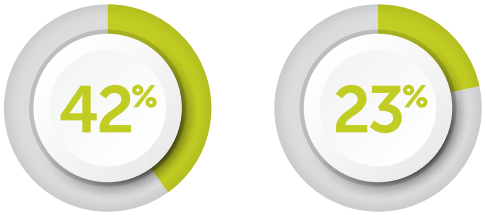
OHE may result in permanent cognitive deficits and reduced survival rate[10-12]

Multiple episodes of OHE are associated with persistent deficits in[10]:

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

Severity of cognitive impairment increased with the number of previous episodes of OHE.[10]

Patient survival rates from time of OHE diagnosis[11]



1-year survival rate†

3-year survival rate

Data from analysis published in 1999.
†1-year survival rates have been reported to be between 36% and 42%.[11,12]

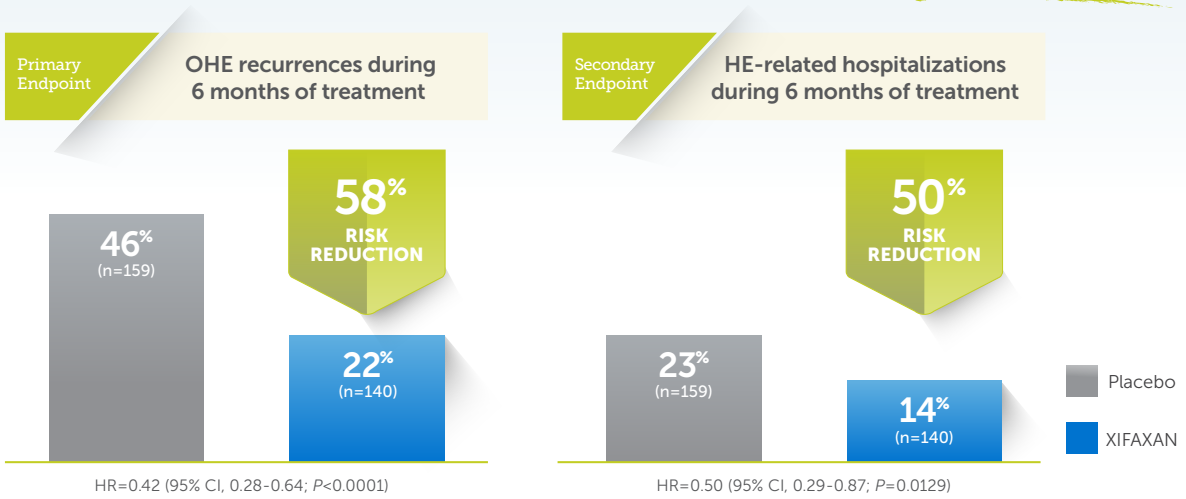
How to spot OHE

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

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

In a clinical trial of adults

XIFAXAN cut the risk of OHE recurrence and HE-related hospitalizations in half[2]



91% of patients in the placebo and XIFAXAN groups were on lactulose[2]

Study design[2,13]

- In a randomized, placebo-controlled, double-blind, multicenter, multinational, 6-month study, the efficacy of XIFAXAN 550 mg (taken orally twice a day) was evaluated in 299 adult subjects
- **Inclusion criteria:** Currently in remission (Conn score of 0 or 1) from HE and ≥2 episodes of HE associated with chronic liver disease in the previous 6 months
- **Primary endpoint:** Time to first breakthrough overt HE episode, defined as a marked deterioration in neurological function (an increase in Conn score to grade ≥2 or an increase in Conn score and asterixis grade of 1 each if subject entered study at grade 0)
- **Key secondary endpoint:** HE-related hospitalization

Safety from 6-month double-blind study[2]

91% of patients were on lactulose	Peripheral edema	Nausea	Dizziness	Fatigue	Ascites
XIFAXAN % (n=140)	**15% (21)**	**14% (20)**	**13% (18)**	**12% (17)**	**11% (16)**
Placebo % (n=159)	8% (13)	13% (21)	8% (13)	11% (18)	9% (15)

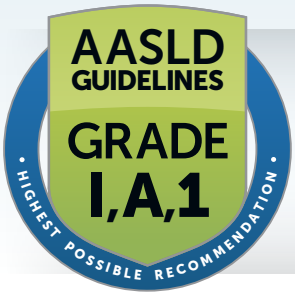
Percentage of HE patients taking XIFAXAN, with adverse reactions occurring at an incidence of ≥10% and at a higher rate than placebo in a randomized, double-blind, multicenter clinical trial.[2]

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 accompanying full Prescribing Information.

Align with the guidelines for patients at risk



XIFAXAN earned AASLD/EASL's highest possible recommendation* (GRADE I,A,1) as an add-on therapy to lactulose to reduce the risk of overt HE recurrence after a patient has a recurrence while on lactulose alone.[1]

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.

For patients with overt HE, XIFAXAN dosing is convenient

One 550 mg tablet, twice daily—no dose adjustments or titrations needed[2]

- 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**[2]

Can be continued for as long as patient is at risk of recurrent OHE[2]

ICD-10 codes for overt HE[14†]	
K72.90 and K72.91	Hepatic failure, unspecified. Indicate lactulose history if applicable

[†]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.
- In a clinical study, the most common adverse reactions for XIFAXAN in HE (≥10%) were peripheral edema (15%), nausea (14%), dizziness (13%), fatigue (12%), and ascites (11%).

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

References: 1. 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. **2.** XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals. **3.** Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: a population-based study. *J Clin Gastroenterol.* 2015;49(8):690-696. **4.** Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015;148(3):547-555. **5.** Kim D, Li AA, Gadiparthi C, et al. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. *Gastroenterology.* 2018;155(4):1154-1163. **6.** Murphy S, Xu J, Kochanek KD, Arias E, Tejada-Vera B. Deaths: final data for 2018. *Natl Vital Stat Rep.* 2021;69(13):1-83. **7.** Tapper EB, Henderson JB, Parikh ND, et al. Incidence of and risk factors for hepatic encephalopathy in a population-based cohort of Americans with cirrhosis. *Hepatol Commun.* 2019;3(11):1510-1519. **8.** Healthcare Cost and Utilization Project. Overview of the Nationwide Readmissions Database (NRD). https://www.hcup-us.ahrq.gov/nrdoverview.jsp. Accessed August 19, 2016. **9.** Data on file. Salix Pharmaceuticals. Bridgewater, NJ. **10.** Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology.* 2010;138(7):2332-2340. **11.** Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol.* 1999;30(5):890-895. **12.** 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. **13.** Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071-1081. **14.** ICD-10. Centers for Medicare & Medicaid Services. www.cms.gov/Medicare/Coding/ICD10. Accessed August 7, 2020.

Xifaxan® rifaximin 550 mg tablets

For multiple symptom relief for adults with IBS-D

Prescribe XIFAXAN[2]

In a US clinical trial

The majority of IBS-D patients had an abnormal composition of bacteria in the gut[12]

- 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[2,9,12,33-36]

Mechanism of action is unknown and does not imply clinical efficacy.

Short-term therapy.[2*] Lasting relief.[2†]

- Just 2 weeks* of XIFAXAN provided up to 6 months of lasting relief from abdominal pain and diarrhea† and significant relief of bloating and urgency[2,13,37‡]

*Patients who experience recurrence can be retreated up to 2 times.
†Median of 10 weeks (range of 6 to 24 weeks).
‡See study designs and results on pages 6-8.

Excellent insurance coverage[38]

- 98% of commercially insured patients have coverage for XIFAXAN[38§‖]
- 96% of Medicare patients have coverage for XIFAXAN[38§‖]
- 90% of eligible¶, commercially insured patients who had coverage for XIFAXAN paid $10 or less for their prescription when a copay card or eVoucher was applied in 2020[38]

§Formulary status subject to change.
‖See ICD-10 code disclaimer on Dosing page.
¶See eligibility criteria on Copay page.

INDICATIONS

XIFAXAN® (rifaximin) 550 mg tablets are indicated for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults and 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.
- *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 accompanying full Prescribing Information.

Salix® Pharmaceuticals

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