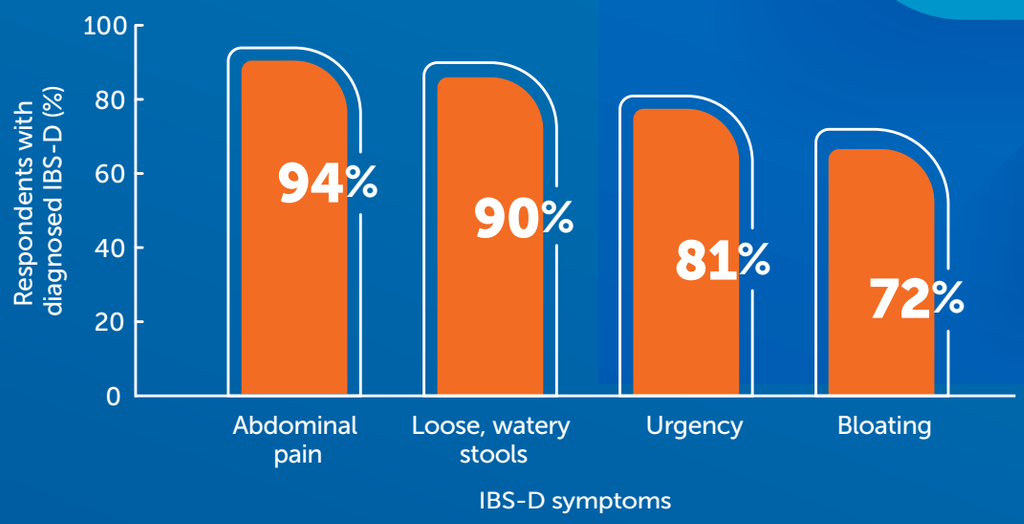
Majority of IBS-D patients may suffer with multiple symptoms[1]

More than 70% of patients suffered from multiple IBS-D symptoms in a 12-month period[1]*

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[1]*



IBS-D=irritable bowel syndrome with diarrhea

*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.

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.
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
- There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering XIFAXAN to these patients.
- Caution should be exercised when concomitant use of XIFAXAN and P-glycoprotein (P-gp) and/or OATPs inhibitors is needed. Concomitant administration of cyclosporine, an inhibitor of P-gp and OATPs, significantly increased the systemic exposure of rifaximin. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to rifaximin.

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

Xifaxan® rifaximin 550 mg tablets

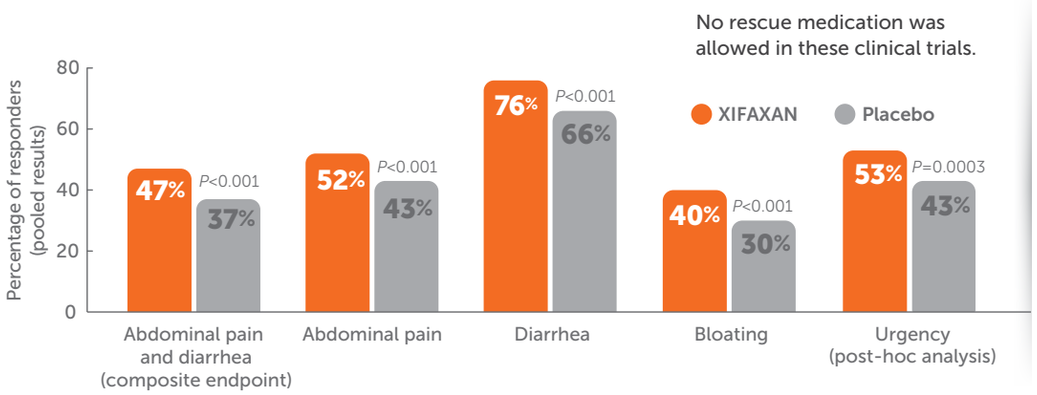
In adults with IBS-D in TARGET 1 and 2

Just 2 weeks of XIFAXAN provided significant relief of multiple IBS-D symptoms[2-4]*

*Patients who experience recurrence can be retreated up to 2 times.[2]
†Based on aggregated total of all gastroenterologists as of February 2021.

Xifaxan® rifaximin 550 mg tablets

Gastroenterologists' #1 prescribed medication approved for IBS-D[5†]



TARGET 1 and 2 study design

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.[2,3]

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.[6]

IBS-D=irritable bowel syndrome with diarrhea

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]."*[2,3]

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.[2,3]

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.[2,3]

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.[3]

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]."*[3‡]

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]."* Percentage of urgency responders based on weekly responses in TARGET 1 and 2 in a pooled post hoc analysis.[4]

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

Well-established safety profile[2]

Side effects at rates similar to placebo[2]

Adverse event	TARGET 1 & 2 XIFAXAN (n=624)	TARGET 1 & 2 Placebo (n=634)	TARGET 3 XIFAXAN (n=328)	TARGET 3 Placebo (n=308)
Nausea	3%	2%	2%	1%
Alanine aminotransferase (ALT) increased§	NA	NA	2%	1%

- Constipation was observed in only 0.5% of XIFAXAN patients[6]
- Did not cause any clinically relevant antibiotic resistance after 1 to 3 treatment cycles[7]
  - *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

§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.

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

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. American Gastroenterological Association. IBS in America: survey summary findings. December 2015. Accessed March 31, 2021. http://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/docs/survey-findings-pdf-635473172.pdf. **2.** XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals. **3.** Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med*. 2011;364(1):22-32. **4.** Pimentel M, Cash BD, Lacy BE, et al. Assessing the efficacy of rifaximin in diarrhea-predominant irritable bowel syndrome: a post hoc analysis of two phase 3, randomized, placebo controlled trials. Poster presented at: World Congress of Gastroenterology; October 13-18, 2017; Orlando, FL. **5.** IQVIA Xponent. February 2021. **6.** Data on file. Salix Pharmaceuticals. Bridgewater, NJ. **7.** 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.

Salix Pharmaceuticals
400 Somerset Corporate Blvd., Bridgewater, NJ 08807