SPECIAL REPORT

Diagnostic Recommendations for IBS-D and Treatment Using Rifaximin: Real-World Perspectives

This resource was developed and sponsored by Salix Pharmaceuticals.

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This Special Report features real physicians who have been compensated by Salix Pharmaceuticals for their participation. The content is based on their own personal experiences.

Inside

Key Highlights

- Irritable bowel syndrome with diarrhea (IBS-D) is a common disorder of gut-brain interaction characterized by recurrent abdominal pain associated with defecation and frequent, loose stools.[1,2]
- IBS-D has a multifactorial etiology that includes an altered gut microbiome (gut dysbiosis).[1,2]
- The ACG Clinical Guideline for the Management of IBS suggests a positive diagnostic strategy for IBS-D (rather than a diagnosis of exclusion) for patients with symptoms of IBS to improve time to initiate appropriate therapy.[2]
- XIFAXAN® (rifaximin) is an FDA-approved nonsystemic antibiotic for IBS-D.[3]
  - There is an increased systemic exposure in patients with severe (Child-Pugh Class C) hepatic impairment. Caution should be exercised when administering rifaximin to these patients.[3]
- Rifaximin 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.[3-7]
- The ACG Clinical Guideline includes a strong recommendation* for rifaximin to treat global IBS-D symptoms (based on moderate quality† of evidence).[2]

ACG, American College of Gastroenterology.

*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.[2]

†Summary of quality of evidence: High=The estimate of effect is unlikely to change with new data; Moderate=Estimate of effect is very uncertain.[2]

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.

DIAGNOSIS OF IBS-D AND INTRODUCTION TO RIFAXIMIN

Introduction

Irritable bowel syndrome with diarrhea (IBS-D) is a chronic disorder of gut-brain interaction characterized by abdominal pain and frequent, loose stools for which a distinct isolated structural pathology is not identified.[1,2] Additional symptoms may include urgency and abdominal bloating, which is present in the majority of patients.[1] IBS-D is the most common subtype of IBS in the United States and has a multifactorial, evolving pathophysiology with mechanistic underpinnings including alterations in visceral sensitivity, gut microbial alterations and dysbiosis, increased intestinal epithelial permeability, disrupted motility, and immune and neural-hormonal system involvement.[1,8]

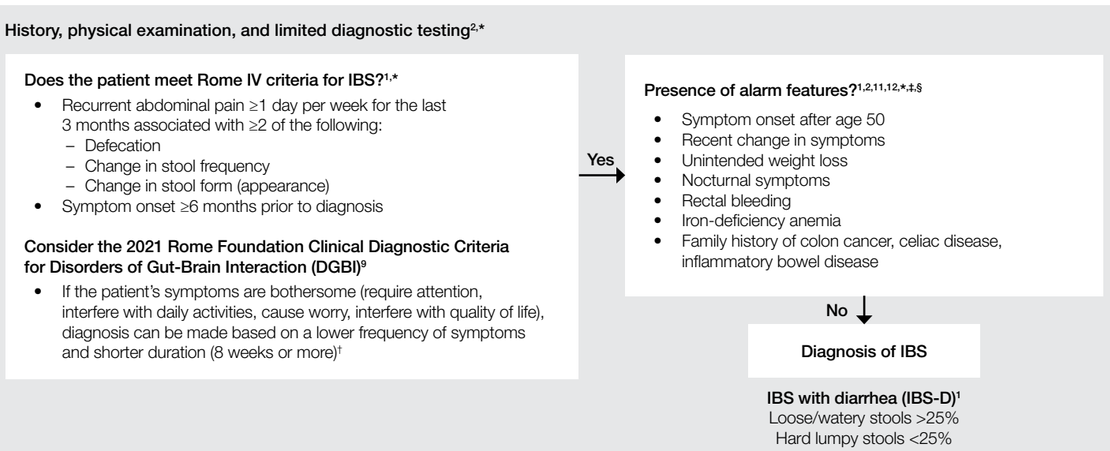
Making a Positive Diagnosis

The American College of Gastroenterology (ACG) Clinical Guideline for the Management of Irritable Bowel Syndrome suggests a positive IBS-D diagnostic strategy (rather than diagnosis of exclusion) to improve the time to initiate appropriate therapy. The ACG recommends this approach as an effort to minimize unnecessary diagnostic testing and reduce healthcare costs.

Making a positive diagnosis of IBS-D requires a detailed clinical history and physical examination, with limited diagnostic testing (**Figure 1**).[2] The Rome IV clinical criteria for IBS are based on the presence and history of abdominal symptoms. For a diagnosis of IBS, recurrent abdominal pain must be present at least 1 day per week for the last 3 months and is related to ≥2 of the following: defecation, change in stool frequency, and change in stool form in the absence of alarm features (eg, unintended weight loss, rectal bleeding, family history of colon cancer). Symptom onset must have occurred ≥6 months prior to diagnosis. For patients with IBS-D, most abnormal bowel movements consist of loose, watery stools.[1]

Clinicians should also consider the recommendation from the 2021 Rome Foundation Clinical Diagnostic Criteria for Disorders of Gut-Brain Interaction that if a patient's symptoms are bothersome (eg, require attention, interfere with daily activities, cause worry, interfere with quality of life), a diagnosis can be made with lower frequency of symptoms and shorter duration (≥8 weeks), if there is clinical confidence that other diagnoses have been sufficiently ruled out based on presentation and other investigations as needed.[9] Optimal diagnostic and therapeutic strategies for IBS-D management consider the multisymptom burden to the patient.[10]

Figure 1. Making a Positive Diagnosis of Irritable Bowel Syndrome (IBS)



*Specific laboratory and diagnostic testing recommendations have been proposed by the American College of Gastroenterology's (ACG) 2020 Clinical Guideline: Management of Irritable Bowel Syndrome, as well as by the American Gastroenterological Association's (AGA) 2019 Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). These testing recommendations may help clinicians choose appropriate tests to exclude other diagnoses in the setting of suspected IBS.[2,13]

†Provided that there is clinical confidence that other diagnoses have been sufficiently ruled out based on presentation and additional investigations as needed.[9]

‡If yes, consider other organic pathology; additional testing may be indicated.[2,13]

§This is not an all-inclusive list of alarm features.

IMPORTANT SAFETY INFORMATION

- *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.

Rifaximin for the Treatment of IBS-D

XIFAXAN® (rifaximin) is a nonsystemic antibiotic (<0.4% is absorbed from the gastrointestinal tract) FDA approved for the treatment of adults with IBS-D.[3] Rifaximin blocks one of the steps in the transcription of bacterial DNA to RNA, inhibiting protein synthesis and bacterial growth. It is administered as a 2-week treatment course (550-mg tablet 3 times daily); patients may receive up to 2 additional rifaximin courses if symptoms relapse.[3]

The ACG Clinical Guideline for the Management of Irritable Bowel Syndrome includes a strong recommendation* for rifaximin to treat global IBS-D symptoms (based on moderate quality† of evidence).[2]

*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.[2]

†Summary of quality of evidence: High=The estimate of effect is unlikely to change with new data; Moderate=Estimate of effect is very uncertain.[2]

Efficacy

In two identically designed randomized, double-blind, placebo-controlled clinical studies conducted over a period of 3 months (TARGET 1 and TARGET 2), 1258 patients with IBS-D (according to Rome II criteria) were treated with rifaximin 550 mg 3 times daily (n=624) or placebo (n=634) for 14 days. A total of 41% of patients (n=254/624) receiving rifaximin 550 mg in both studies, 31% (n=98/314) of patients receiving placebo in TARGET 1, and 32% (n=103/320) of patients receiving placebo in TARGET 2 experienced adequate relief of IBS-D signs and symptoms for at least 2 of 4 weeks during the month following treatment. Adequate relief was 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]."[3,14]

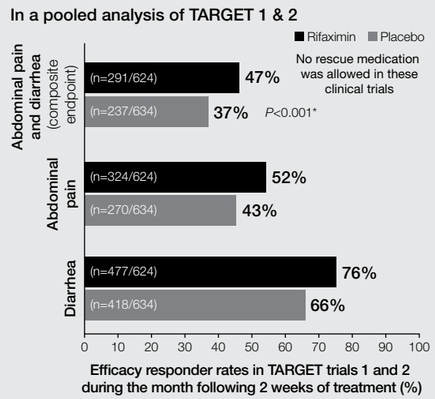
In a pooled analysis of these two studies, 47% of patients treated with rifaximin compared with 37% of those treated with placebo had significant improvement in both abdominal pain and diarrhea ($P<0.001$) according to the composite endpoint (≥30% decrease from baseline in weekly mean abdominal pain, with a weekly mean stool consistency score of <4 [loose stool] for ≥2 weeks during the month following 2 weeks of treatment) (**Figure 2**).[3,14]

Retreatment

The safety and efficacy of retreatment with XIFAXAN® (rifaximin) in patients with IBS-D (according to Rome III criteria) were evaluated in a two-phase trial (TARGET 3) consisting of an open-label treatment phase and a randomized, double-blind, placebo-controlled retreatment phase.[3,15]

The primary endpoint was the proportion of patients with symptom recurrence who were responders to retreatment in both IBS-D–related abdominal pain and stool consistency during the 4 weeks following the first retreatment with rifaximin. Abdominal pain response was defined as ≥30% decrease from baseline in weekly mean abdominal pain score. Stool consistency response was defined as ≥50% decrease from baseline in number of days/week with Bristol Stool Form Scale (BSFS) type 6 or 7 (mushy or watery) stool consistency.[3,15]

Figure 2. Relief From Abdominal Pain and Diarrhea With 2-Week Rifaximin Treatment[3,14]



*$P<0.001$, represents pooled data.

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 rifaximin 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 rifaximin 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 rifaximin 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).

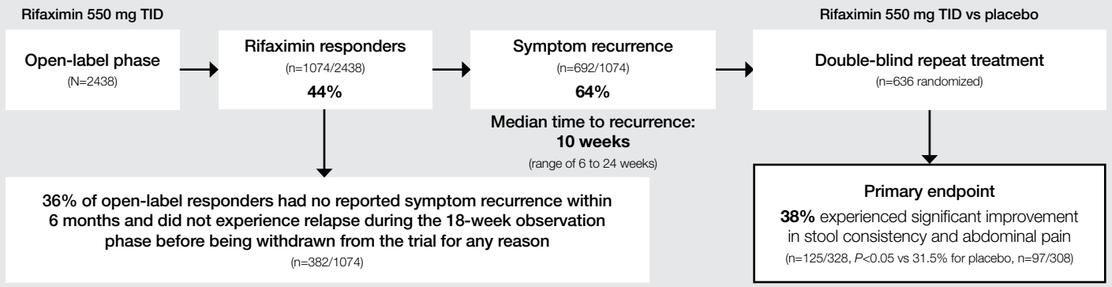
Composite endpoint: ≥30% decrease from baseline in weekly mean abdominal pain, with a weekly mean stool consistency score of <4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment.

IMPORTANT SAFETY INFORMATION

- 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.

A total of 44% (n=1074/2438) of patients were open-label responders to XIFAXAN® (rifaximin); 36% (n=382/1074) of initial rifaximin responders had no reported symptom recurrence within 6 months (**Figure 3**). Initial responders with symptom recurrence (return of abdominal pain or lack of stool consistency for ≥3 weeks during a 4-week follow-up period) entered a randomized, double-blind, placebo-controlled repeat treatment phase, wherein a significantly higher percentage of responders were observed with rifaximin retreatment (n=125/328) versus placebo treatment (n=97/308) for 2 weeks (38% vs 31.5%, respectively; *P*<0.05).[3,15]

Figure 3. TARGET 3 Study Design and Efficacy of Retreatment With Rifaximin[3,15]



TID, three times daily.

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 rifaximin in patients with IBS-D who had responded to a 2-week course of rifaximin 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 weeks 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.
- Responders showing symptom recurrence entered the double-blind repeat treatment phase of the study, where patients were randomly assigned (1:1) to receive 2 repeat treatment courses of rifaximin or placebo for 14 days. The second retreatment was initiated 10 weeks after the first retreatment.
- **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.**

Safety

Across all studies, adverse reactions reported with XIFAXAN® (rifaximin) treatment were comparable to those reported with placebo (**Table 1**).[3] Constipation was observed in 0.3%-0.6% of patients treated with rifaximin.[15,16] An analysis of stool microbial species showed no clinically relevant antibiotic resistance after 1 to 3 treatment cycles.[17]

Table 1. Adverse Reactions Occurring in ≥2% in Rifaximin-Treated Patients and at a Higher Rate Than Placebo[3]

	TARGET 1 & 2		TARGET 3	
Adverse reaction	**Rifaximin (n=624)**	**Placebo (n=634)**	**Rifaximin (n=328)**	**Placebo (n=308)**
Nausea	3%	2%	2%	1%
ALT increased*	NA	NA	2%	1%

ALT, alanine aminotransferase; NA, not applicable.
*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.[18]

Summary

Making a positive diagnosis of IBS-D requires a detailed clinical history and physical examination, with limited diagnostic testing.[2] Optimal diagnostic and therapeutic strategies for IBS-D management consider the multisymptom burden to the patient.[10]

XIFAXAN® (rifaximin) is FDA approved for the treatment of adults with IBS-D, administered as a 2-week treatment course (550-mg tablet three times daily); patients may be retreated up to 2 times if symptoms relapse.[3] The ACG Clinical Guideline for the Management of Irritable Bowel Syndrome includes a strong recommendation* for rifaximin to treat global IBS-D symptoms (based on moderate quality† of evidence).[2]

*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.[2]

†Summary of quality of evidence: High=The estimate of effect is unlikely to change with new data; Moderate=Estimate of effect is very uncertain.[2]

IMPORTANT SAFETY INFORMATION

- 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.

CLINICAL HIGHLIGHT #1: Diagnosis and Treatment of IBS-D in a Tertiary Medical Center

Mark Pimentel, MD

As an expert in gastric motility for more than 25 years, Dr. Pimentel has extensive experience in the diagnosis and treatment of IBS-D. He is currently the Executive Director of the Medically Associated Science and Technology (MAST) Program at Cedars-Sinai in Los Angeles, California, which focuses on the development of drugs related to conditions of the microbiome, and continues to treat patients with IBS-D.

In Dr. Pimentel's experience, several factors may contribute to underdiagnosis or delayed diagnosis of IBS-D. The lack of extensive research in IBS-D results in self-management of symptoms by patients through methods such as diet restriction and use of probiotics, over-the-counter medications, or supplements that may not be beneficial. Many patients also have lived with their condition for so long that they do not realize their symptoms are due to a medical condition.[19] In addition, symptoms of IBS-D may fluctuate, and the occurrence of "good days" may delay patients' interest in seeking treatment.[10,20] According to the Rome IV criteria, experiencing abdominal pain once a week for 3 months may signal IBS-D when associated with a change in stool frequency or appearance.[1]

"Having abdominal pain and diarrhea once a week is totally not normal, but…many people convince themselves that's just the normal way they are."[1]

Certain healthcare professionals encountered during a patient's journey may also contribute to a delay in diagnosis of IBS-D.[19] According to Dr. Pimentel, physicians had traditionally been "often dismissive of IBS…it was almost treated as a lifestyle illness." On the other end of the spectrum, some practitioners worry about missing a potentially serious diagnosis.[19] "Physicians need to be more confident in their ability to diagnosis this condition. It's important to instill confidence in your patients…and to gain that trust."[2]

When a patient presents with abdominal pain, Dr. Pimentel considers their clinical history, including asking patients specifically about other IBS-D symptoms, the most important component of an accurate IBS-D diagnosis. In a patient who fulfills the Rome IV criteria, Dr. Pimentel assesses for any alarm symptoms, such as blood in the stool, weight loss, and nocturnal diarrhea, to rule out other conditions. He then conducts a thorough physical examination, which helps to reassure patients as well as to exclude any organic etiology of their symptoms.[1]

Dr. Pimentel mostly avoids the use of antispasmodics in the management of IBS-D, which is in alignment with the current ACG Guideline recommendation (not recommended based on a low quality of evidence).[2] In Dr. Pimentel's clinical experience, XIFAXAN® (rifaximin) is often his prescription of choice because it is FDA approved for the treatment of adults with IBS-D, and he has seen success with the use of rifaximin in his patients.[3]

Microbiome data from adults with IBS-D indicate that rifaximin modulates specific bacteria groups in the gut. Multiple rifaximin treatment cycles show only a modest, transient decrease in overall gut bacteria.[7]

Rifaximin inhibits bacterial protein synthesis and consequently inhibits the growth of bacteria.[3]

Results from the large-scale, randomized, controlled clinical trials assessing the efficacy and safety of rifaximin in IBS-D—the TARGET trials—are also a major reason for Dr. Pimentel's decision to start with rifaximin in his patients with IBS-D. "For the IBS-D patients in the trials, abdominal pain improved and stool consistency improved…using challenging FDA endpoints." What makes this treatment for IBS-D stand out for Dr. Pimentel is twofold – the ability of rifaximin to address multiple symptoms of IBS-D, and the short treatment duration.[3,14] Patients take rifaximin for only 2 weeks, with some showing responses for months after.[3]

After prescribing rifaximin for his adult patients with IBS-D, Dr. Pimentel schedules a follow-up within 3 weeks, and a second follow-up in another 3 weeks. For patients who have experienced successful amelioration of symptoms, he typically waits 2 to 3 months to evaluate whether the patient's symptoms are still effectively managed.[3] In general, frequent patient visits allow Dr. Pimentel to verify what lifestyle changes or medications were helpful or not helpful. If a patient has a relapse of IBS-D symptoms after 3 to 6 months, Dr. Pimentel re-treats with rifaximin. "The TARGET 3 trial showed that if a patient had a relapse, you could re-treat up to two times with rifaximin."[3]

The safety and efficacy demonstrated in the TARGET clinical trials, including efficacy for some of the multiple symptoms patients with IBS-D experience, influence Dr. Pimentel's use of rifaximin as his treatment of choice for patients with IBS-D.[3,14,15] Additional reasons Dr. Pimentel chooses rifaximin are the 2-week treatment course, the ability for retreatment, and the fact that rifaximin is the only therapy that targets a potential underlying factor of IBS-D.[3]

IMPORTANT SAFETY INFORMATION

- 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 click here for full Prescribing Information.

CLINICAL HIGHLIGHT #2: Diagnosis and Treatment of IBS-D in a Digestive Health Center

Amy Kassebaum-Ladewski, PA-C, RD, MMS

At Northwestern Memorial Hospital, Amy Kassebaum-Ladewski is a physician assistant (PA) specializing in gastroenterology who mostly sees patients with gastric motility issues, including IBS-D. In her experience, patients have often been suffering from symptoms for several years before receiving an IBS-D diagnosis. "These patients often present with chronic diarrhea, abdominal pain, and discomfort, which can be highly disruptive."[1,19]

According to Ms. Kassebaum-Ladewski, patients presenting with symptoms of IBS-D often fear a more serious diagnosis, and some may have difficulty accepting a diagnosis of IBS-D.[2,12] It is therefore extremely important for providers to understand the Rome IV criteria and feel confident making an IBS-D diagnosis. When a patient meets the Rome IV criteria for IBS-D and has no relevant alarm symptoms, Ms. Kassebaum-Ladewski feels confident in making an IBS-D diagnosis.[2] She is a strong proponent of spending a longer time with patients to obtain a thorough clinical history that can lead to an accurate diagnosis, and is hopeful that increased education on how to diagnose IBS will allow for the initiation of appropriate therapies without a diagnostic delay.[2,21]

"Once they meet the Rome IV criteria and alarm features are ruled out, it's important to delve a little bit more—make sure you're not missing other components."[2,21]

XIFAXAN® (rifaximin) is Ms. Kassebaum-Ladewski's recommended treatment choice for IBS-D because of its ability to treat IBS-D and some of its associated symptoms, which is supported by the results of multiple clinical trials.[3,14,15] In addition, rifaximin has a short treatment course.[3] "It's just a 2-week course—many patients are very open to trying it because it is not long-term management and offers the potential for significant improvement."[3,14,15] Although patients with IBS-D successfully treated with rifaximin might have symptoms return, Ms. Kassebaum-Ladewski is confident in retreatment.[3] She schedules regular follow-ups with her patients directly following the completion of the 2-week treatment to assess response. She also evaluates whether symptoms have relapsed following an initial response to rifaximin, indicating the potential need for retreatment.[3]

"I counsel my patients that IBS-D is a chronic condition, and that rifaximin has the option for retreatment up to two times if symptoms recur."[2,3]

With her credentials as a registered dietician, Ms. Kassebaum-Ladewski also sees diet alterations as useful for some IBS-D patients. "I may start with more basic interventions like avoiding caffeine, alcohol, and high-fat meals; or I might emphasize the timing of meals and eating more balanced meals. If bloating, gas, diarrhea, discomfort are still primary symptoms, that's when I would talk with them about the low FODMAP diet and make sure that's guided under the direction of a well-trained GI dietitian."[2] Ms. Kassebaum-Ladewski will not usually implement a dietary intervention while a patient is on prescription treatment for IBS-D in order to assess the effectiveness of therapy; however, some unresolved symptoms (eg, bloating, loose stools) during treatment may motivate consideration of dietary triggers.

Ultimately, Ms. Kassebaum-Ladewski wants her adult patients with IBS-D to feel as though they have control over their IBS-D and some of its symptoms.[3,14] XIFAXAN® (rifaximin) has been shown to provide symptom relief with a single 2-week treatment course and can be repeated up to 2 times in the future if IBS-D symptoms recur.[3]

IMPORTANT SAFETY INFORMATION

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

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.
- 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 click here for full Prescribing Information.

REFERENCES

1. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393-1407.
2. Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol.* 2021;116(1):17-44.
3. XIFAXAN [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals.
4. Soldi S, Vasileiadis S, Uggeri F, et al. Modulation of the gut microbiota composition by rifaximin in non-constipated irritable bowel syndrome patients: a molecular approach. *Clin Exp Gastroenterol.* 2015;8:309-325.
5. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother.* 2008;20(2):186-194.
6. Zeber-Lubecka N, Kulecka M, Ambrozkiewicz F, et al. Limited prolonged effects of rifaximin treatment on irritable bowel syndrome-related differences in the fecal microbiome and metabolome. *Gut Microbes.* 2016;7(5):397-413.
7. Fodor AA, Pimentel M, Chey WD, et al. Rifaximin is associated with modest, transient decreases in multiple taxa in the gut microbiota of patients with diarrhoea-predominant irritable bowel syndrome. *Gut Microbes.* 2019;10(1):22-33.
8. Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology.* 2020;158(5):1262-1273.e3.
9. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology.* 2022;162(3):675-679.
10. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA.* 2015;313(9):949-958.
11. Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology.* 2022;163(1):137-151.
12. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. *United Eur Gastroenterol J.* 2017;5(6):773-788.
13. Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). *Gastroenterology.* 2019;157(3):851-854.
14. 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.
15. 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.
16. Schoenfeld P, Pimentel M, Chang L, et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther.* 2014;39(10):1161-1168.
17. 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.
18. Data on file. Salix Pharmaceuticals. Bridgewater, NJ.
19. Sayuk GS, Wolf R, Chang L. Comparison of symptoms, healthcare utilization, and treatment in diagnosed and undiagnosed individuals with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2017;112(6):892-899.
20. American Gastroenterological Association. IBS in America: survey summary findings. December 2015. Accessed March 23, 2023. http://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/docs/survey-findings-pdf-635473172.pdf
21. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology*. 2016;S0016-5085(16)00223-7.

SPECIAL REPORT

Salix Pharmaceuticals

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