

Rifaximin (XIFAXAN) for Irritable Bowel Syndrome with Diarrhea

National Drug Monograph

March 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Minimally absorbed, broad-spectrum antibacterial that inhibits bacterial RNA synthesis. The specific mechanism of action of rifaximin in irritable bowel syndrome (IBS) has not been determined. The most likely mechanism of rifaximin is reduction in overall bacterial load, particularly in the large bowel ¹ ; however, rifaximin also seems to modulate gut microenvironment and produce cytoprotective effects. ²
Indication(s) Under Review in this Document	Treatment of IBS with diarrhea (IBS-D) in adults
Dosage Form(s) Under Review	550 mg tablet
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input type="checkbox"/> Postmarketing Requirements
Pregnancy Rating	No data available on pregnant women to inform any drug associated risks.

Executive Summary

Efficacy	<ul style="list-style-type: none"> Rifaximin had a small, statistically significant beneficial effect relative to placebo in global IBS symptom response using pooled data: 40.7% vs. 31.7%, with a difference of 9.0 percentage points, $p < 0.001$; NNT = 11. Rifaximin had a small, statistically significant beneficial effect relative to placebo in terms of the response rate for adequate relief of bloating (the key secondary efficacy measure): 40.2% vs. 30.3%, difference of 9.9 percentage points, $p < 0.001$; NNT = 10 (pooled results). Relief in the composite end point of abdominal pain and discomfort and relief of loose or watery stools was experienced in a significantly greater percentage of rifaximin patients than placebo patients: 46.6% vs. 38.5% ($p = 0.04$) in TARGET 1 and 46.7% vs. 36.3% ($p = 0.008$) in TARGET 2. Analyses of durability of response showed that a 2-week course of rifaximin was significantly better than placebo in relief of IBS symptoms for 2.5 to 3 months.
Safety	<ul style="list-style-type: none"> In pooled analyses of Phase II and III trial safety data, the adverse event and tolerability profile of rifaximin was similar to that of placebo. A withdrawal due to adverse event occurred for every 846 IBS-D patients who benefited from rifaximin. Based on analyses of stool samples from a random selection of 100 patients in the TARGET 3 trial, there were no clinically relevant changes in bacterial sensitivity to other antibiotic classes, no microbiota alterations, no development of pathogenic bacteria and no opportunistic infections. In IBS-D clinical trials of rifaximin, the incidence of <i>C. difficile</i> colitis was zero per 61.3 patient-years of exposure.
Projected Place in Therapy	<ul style="list-style-type: none"> The American Gastroenterology Association (AGA, 2014) gives a conditional recommendation to use rifaximin (over no drug treatment) in patients with IBS-D (moderate quality evidence [QE]). Rifaximin for IBS should be restricted to patients who have the IBS-D subtype and have not responded to effective and less costly symptom-based alternative therapies.

Background**Purpose for Review**

FDA approval for IBS-D.
Previously reviewed for traveler's diarrhea (2004 monograph, archived) and hepatic encephalopathy (2010 criteria for use).

Issues to be determined:

- ✓ Evidence of need for IBS-D
- ✓ Does rifaximin offer advantages to currently available alternatives?
- ✓ Does rifaximin offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does rifaximin have specific characteristics best managed by the nonformulary process, prior authorization, criteria for use?

Other Therapeutic Options

Nonpharmacologic options include dietary modification, probiotics and physical activity. Gluten avoidance is a dietary modification suggested for IBS-D.

Pharmacologic options are often used complementarily rather than as alternatives.

Formulary Options	Other Considerations	Clinical Guidance
<i>Antibiotics</i>		
Neomycin tab	Improved global IBS symptoms in one placebo-controlled RCT (NNT = 5 at 7 days; N = 111) ³ Use is limited by significant adverse effects. This agent is the only evidence-supported antibiotic alternative to rifaximin.	Lower quality evidence than with rifaximin. Need further, long-term studies before neomycin can be recommended for continuous or intermittent use. ⁸
<i>Antidepressants</i>		
Tricyclics		
Amitriptyline tab	Slows intestinal transit. TCAs improve pain and global symptoms of IBS (NNT = 4), based on a 2011 Cochrane review. ⁴ NNT from a 2012 systematic review / meta-analysis was 8 (3.7–71.9). ⁵	For persistent abdominal pain despite antispasmodics. ⁶ Start at low doses for IBS. If intolerant to one TCA, patient may be tried on a second TCA.
Clomipramine cap		
Desipramine tab		
Doxepin cap, oral liquid		
Imipramine tab		
Nortriptyline cap, soln		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram tab, soln	Inconsistent efficacy results among trials; however, meta-analytic subgroup analyses showed SSRIs improve global assessment scores. ⁴ Treatment effects may be similar to those of TCAs. ⁷	For co-morbid anxiety or depression. May be used to relieve abdominal pain in patients intolerant or not responding to TCAs.
Escitalopram tab		
Fluoxetine cap, soln		
Paroxetine tab		
Sertraline tab, soln		
<i>Antidiarrheals</i>		
Loperamide cap, oral liquid	Improves stool frequency and consistency, but is not beneficial for bloating, abdominal discomfort, or global IBS symptoms, and lacks safety and tolerability data. ⁸	Primarily used for diarrhea, urgency or incontinence.
<i>Antispasmodics</i>		
Dicyclomine tab, cap, soln	Approved for functional bowel / IBS. The only antispasmodic shown to be effective for IBS in a Cochrane review. ⁴ Used at higher doses in IBS-D and may cause dose-related adverse effects.	Primarily used to relieve pain or postprandial urgency.
<i>Bile Acid Sequestrants (BASs)</i>		
Cholestyramine oral powder	Gastrointestinal adverse effects (bloating, flatulence, abdominal discomfort, constipation) limit use of these agents.	For patients with persistent diarrhea despite antidiarrheals. ⁶
Colestipol oral granules for reconstitution		
<i>5-Hydroxytryptamine-3-receptor Antagonists</i>		
Ondansetron inj, tab	Off-label use. One RCT (N = 120)	

showed ondansetron (titrated up to 8 mg 3 times daily for 5 weeks) significantly improved stool consistency, frequency and urgency but did not improve abdominal pain.⁹

Nonformulary Options	Other Considerations	Clinical Guidance
<i>Antidepressants</i>		
Tricyclics		
Amoxapine		
Protriptyline		
Trimipramine		
SSRIs		
Fluvoxamine		
<i>Antidiarrheals</i>		
Eluxadoline tab	Improves global symptoms, abdominal pain, stool consistency, frequency of bowel movements, urgency and quality of life. Approved for treatment of adults with IBS-D. Locally acting mu-opioid receptor agonist / delta-opioid receptor antagonist (C-IV). Several contraindications.	
<i>Antispasmodics</i>		
Chlordiazepoxide / Clidinium cap	Unapproved, marketed, Drug Efficacy Study Initiative (DESI) drug classified by FDA as <i>possibly</i> effective as adjunctive therapy in the treatment of IBS (irritable colon, spastic colon, mucous colitis). Final classification of the less-than-effective indication requires further investigation. ¹⁰	Used for IBS associated with anxiety.
Hyoscyamine inj, tab, tab ER 12 h, tab dispersible, tab sublingual, elixir	Differs from products studied in trials. ⁸ Antispasmodics effective as a class.	
Phenobarbital / Hyoscyamine / Atropine / Scopolamine (DONNATAL) elixir tab, tab ER, elixir	Unapproved, marketed, DESI drug classified by FDA as <i>possibly</i> effective as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis). ¹¹ A 1978 article reported phenobarbital / belladonna to be effective in IBS (N = 16). ¹²	Use on an as-needed basis for patients with abdominal pain due to IBS that persists despite treatment for constipation. ⁶
<i>Bile Acid Sequestrants (BASs)</i>		
Colesevelam cap, oral susp, tab	Insufficient evidence to support off-label use for IBS-D (one small, proof-of-concept RCT; N = 24). ¹³	
<i>5-Hydroxytryptamine-3-receptor Antagonists</i>		
Alosetron	Used for pain, urgency or diarrhea. Had been withdrawn from US market because of serious risks (ischemic colitis, complications of severe constipation). Now available via the Alosetron Prescribing Program at doses lower than those previously approved. Improves global IBS response (NNT 8) ¹⁴ and abdominal pain.	Approved for treatment of severe IBS-D in females with symptoms that have lasted for 6 months and who have not responded to all other conventional treatments.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms *rifaximin* and *irritable bowel*. The search was limited to studies performed in humans and published in English. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Randomized controlled trials, prospective long-term (≥ 1 year) studies, and systematic reviews / meta-analyses (SRMAs) published in peer-reviewed journals were included. The FDA Medical Review of rifaximin for IBS-D was not available.

Review of Efficacy

- The efficacy and safety of rifaximin in adults with IBS-D was established in three multicenter, double-blind, placebo-controlled randomized clinical trials (RCTs).¹⁵ In addition, a dose-comparative, Phase IIb RCT provided further efficacy and safety data. Study treatment (rifaximin 550 mg 3 times daily or placebo) was given for 2 weeks then patients were followed up for 10 weeks (12-week study duration) in the two Phase III trials, TARGET 1 and TARGET 2. In the Phase IIb trial, patients were randomized to one of five study treatments that were given for 4 weeks (including a dummy placebo given for 2 weeks in three of the five groups), and follow-up continued post-treatment for 12 weeks (16-week study duration).¹⁵ Two additional Phase II studies (one of which is published¹⁶) showed efficacy and safety results consistent with those of the Phase III trials.²⁰
- In the TARGET 1 and TARGET 2 Phase III clinical trials,¹⁷ provision of treatment was based on the presence of “nonconstipation (Non-C) IBS” symptoms using Rome II diagnostic criteria; patients with constipation during the ≥ 7 -day eligibility period were excluded. The mean age of the study population was about 46 years (89% were less than 65 years), 28% were males, and 91% were white. The study population had 3 bowel movements per day on average and experienced stool urgency about 80% of bowel movement days. Study patients had a history of IBS symptoms for a mean of about 11 years.
 - The primary efficacy measure in TARGET 1 and TARGET 2 was global IBS symptom response, defined as adequate relief (yes or no) for at least 2 of the first 4 weeks post-treatment. Rifaximin had a small, statistically significant beneficial effect relative to placebo in global IBS symptom response using pooled data: 40.7% vs. 31.7%, with a difference of 9.0 percentage points, $p < 0.001$; NNT = 11 (also see Table 1).
 - Rifaximin had a small, statistically significant beneficial effect relative to placebo in terms of the response rate for adequate relief of bloating (the key secondary efficacy measure): 40.2% vs. 30.3%, difference of 9.9 percentage points, $p < 0.001$; NNT = 10 (pooled results).
 - The pooled results from TARGET 1 and TARGET 2 showed that rifaximin was better than placebo in terms of the percentage of patients reporting improvement in daily ratings of IBS symptoms, bloating, abdominal pain and stool consistency (40.2% vs. 29.5%; difference 10.7%; $p < 0.001$).¹⁷
 - Exploratory FDA-required post hoc analyses of pooled data from the two TARGET trials showed a small but statistically significant benefit based on the composite end point consisting of relief (at least 30% reduction from baseline) of abdominal pain and discomfort and relief of loose or watery stools (stool consistency scores of less than 4, indicating more formed stools) for at least 2 of 4 weeks in a given month. Relief in the composite end point of abdominal pain and discomfort and relief of loose or watery stools was experienced in a significantly greater percentage of rifaximin patients than placebo patients: 46.6% vs. 38.5% ($p = 0.04$) in TARGET 1 and 46.7% vs. 36.3% ($p = 0.008$) in TARGET 2.¹⁷
 - Analyses of durability of response showed that a 2-week course of rifaximin was significantly better than placebo in relief of IBS symptoms for 2.5 to 3 months, although the percentage of patients with adequate relief decreased from about 49% at week 2 (end of treatment) to about 35% at week 12 (10 weeks post-treatment). Further data on durability are discussed under the [TARGET 3 trial](#).
- According to a high-quality meta-analysis, five trials (including the TARGET 1 and TARGET 2 major efficacy-safety trials) used global improvement in IBS symptoms as the primary efficacy measure (Table 1).¹⁷

Table 1 Systematic Review of Rifaximin RCTs: Global improvement of IBS symptoms (PEM)

Ref	Design [†]	IBS Subtype	Dose, mg	Duration of Tx / Followup	Response-RIF, n/N (%)	Response-PBO, n/N (%)	ABI, %	NNT	OR	95% CI
Sharara	SC DB	All [‡]	400 b.i.d.	10 d / 10 d	10/37 (27.0)	3/33 (9.1)	17.9	5.6	3.70	0.92–14.89
Pimentel	2C	All	400 t.i.d.	10 d / 10 wk	14/43 (32.6)	4/44 (9.1)	23.5	4.3	4.83	1.44–16.18
Lembo	MC	IBS-D	550 b.i.d.	2 wk / 12 wk	100/191 (52.3)	87/197 (44.2)	8.1	12.3	1.39	0.93–2.07
TARGET 1	MC	Non-C	550 t.i.d.	2 wk / 10 wk	126/309 (40.8)	98/314 (31.2)	9.6	10.4	1.52	1.09–2.11
TARGET 2	MC	Non-C	550 t.i.d.	2 wk / 10 wk	128/315 (40.6)	103/320 (32.2)	8.4	11.9	1.44	1.04–2.00
Pooled			—	—	378/895 (42.2)	295/908 (32.4)	9.8	10.2	1.57	1.22–2.01

Source: Menees, et al (2012)¹⁸

ABI, Absolute benefit increase; PEM, Primary efficacy measure

[†]All studies used Rome II criteria for diagnosis. [‡]20% IBS-D.

- In the pooled analysis of the five trials, rifaximin therapy resulted in a small but statistically significant improvement in global IBS response rates compared with placebo (absolute difference of 9.8 percentage points; NNT 10.2).¹⁸
- Compared with placebo, rifaximin therapy resulted in a small benefit in the percentage of patients with improvement in bloating. The pooled results from 4 RCTs showed that, at 10 to 14 days post-treatment, 357 (41.6%) of 858 patients on rifaximin and 277 (31.7%) of 875 on placebo had improvement in bloating; the difference was 9.9 percentage points; NNT 10.1; OR 1.55 (95% CI 1.23–1.96; $p < 0.001$).
- The outcome measure of improvement in abdominal pain showed mixed results: two trials (Pimentel [2006] and Lembo [2008]) showed no significant difference between rifaximin and placebo, whereas both TARGET 1 and TARGET 2 showed significant differences in terms of improvement in abdominal pain ($p = 0.003$).
- For improvement in stool consistency, results were also mixed: one trial (Lembo [2008]) showed no significant difference between rifaximin and placebo, while TARGET 1 and TARGET 2 showed a benefit with rifaximin in reducing loose or watery stools ($p < 0.001$).
- Age and gender were not predictive of a differential treatment response.
- TARGET 3 was a 51-week, multicenter, double-blind, placebo-controlled randomized trial that assessed the effects of up to two additional repeat treatments with rifaximin in 2579 university hospital patients with IBS-D. Results were presented at the American College of Gastroenterology 2014 Annual Scientific Meeting.^{19, 20}
 - Following an open-label phase consisting of a 2-week treatment course of rifaximin (550 mg 3 times daily) then a 4-week treatment-free period, 42% of patients responded. Response was based on a composite end point: a decrease from baseline of at least 30% in mean abdominal pain score and a decrease from baseline of at least 50% in the number of days per week with a stool consistency of type 6 or 7.
 - In the first retreatment phase, the 636 patients who did not meet the composite end point and had recurrent symptoms in IBS-D were re-randomized to 2-week courses of rifaximin (550 mg) or placebo, then followed for 4 weeks without treatment. Patients started with lower symptom severity scores than they did at baseline. Rifaximin was better than placebo in achieving the composite end point by a difference of 7 percentage points (Table 2).²⁰

Table 2 Repeat Treatment (TARGET 3)

Outcome Measure	RIF 550 T.I.D.	PBO	Diff, %	P-Value	Time Point Post-tx, wk	Comments
Composite Endpoint [†]	125/328 (38)	97/308 (31)	7	<0.05	4	NNT = 14. First retreatment.
Composite Endpoint [†]	(37)	(29)	8	0.04	6	NNT = 13. Second retreatment.
Prevention of recurrence	(13)	(7)	6	0.0068		NNT = 17.
Duration of response	(17)	(12)	5	0.0419		

Sources: Refs 19,20

Values reported as n/N (%).

[†]Decrease from baseline of at least 30% in mean abdominal pain score and a decreased from baseline of at least 50% in the number of days per week with a stool consistency of type 6 or 7.

- The rates of nonrecurrence after the first repeat treatment through the treatment-free follow-up period (10 weeks after the first repeat treatment) were 56 (17.1%) of 328 patients and 36 (11.7%) of 308 patients in the rifaximin and placebo groups, respectively (difference 5.4%; 95% CI 1.2%–11.6%).²⁰
- A second retreatment phase was followed by 6 weeks without treatment. Again, rifaximin was better than placebo in treatment response by a difference of 8 percentage points.¹⁹

- About one-third of patients had no relapse for up to 22 weeks post-treatment.¹⁹ The median time to recurrence for initial responders (i.e., to open-label rifaximin treatment) was 10 weeks (range, 6 to 24 weeks).²⁰
- Durability of IBS Symptom Relief: Overall, the data from the three TARGET trials suggest that symptoms may be relieved for 2.5 to 3 months post-treatment but may recur over 3 to 9 months.⁸
- For indirect comparisons of rifaximin and alternative therapies for IBS-D, see under [Other Safety Considerations](#).

Potential Off-Label Use

- Small intestinal bowel overgrowth (SIBO): UpToDate suggests that rifaximin may be the antibiotic of choice because it may have a lower risk of clinically relevant resistance than other antibiotics. One RCT (N = 142) may support its use.²¹
- Treatment of recurrent *Clostridium difficile* infection in adults: This is based on one published RCT²² and an unpublished RCT.²⁰ Rifaximin is included in the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (SHEA / IDSA) guidelines as an alternative therapy (based on noncontrolled trials and case reports) but without specific recommendations.²³
- Moderately active Crohn’s disease: Rifaximin with extended intestinal release (EIR) showed efficacy in a 12-week, multicenter, double-blind, placebo-controlled RCT (N = 402).²⁴
- Treatment of chronic prostatitis and gastrointestinal symptoms in patients with chronic prostatitis type III: a small, noncontrolled, observational study (N = 16) did not provide sufficient evidence to support the use of rifaximin for this purpose.²⁵
- Treatment of symptomatic uncomplicated diverticular disease (SUDD): According to a systematic review, 9 RCTs have shown that rifaximin used alone or in combination with fiber or mesalamine is efficacious in SUDD; however, only one trial was blinded and long-term (1 year), and further well-designed trials that consider patient diverticular disease history are needed.²⁶ A meta-analysis of four RCTs comparing rifaximin plus fiber with fiber alone concluded that the combination was significantly superior to fiber alone in reducing symptoms and in preventing complications at 1 year in patients with SUDD; however, the benefit in preventing complications may not be clinically important, the number of trials was small and the literature search may have missed trials.²⁷
- Prevention of recurrent diverticulitis: A low-quality, 1-year, multicenter, open-label, proof-of-concept RCT that attempted to evaluate cyclic monthly rifaximin plus fiber versus fiber alone produced inconclusive results.²⁸

Safety

For more detailed information, refer to the prescribing information.

Boxed Warning	• None
Contraindications	• History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the product components
Warnings / Precautions	<ul style="list-style-type: none"> • Not effective for Travelers’ Diarrhea not caused by <i>E. coli</i> • <i>Clostridium difficile</i>-associated diarrhea may occur (monitor) • Use caution in patients with severe (Child-Pugh Class C) hepatic impairment • Use caution if concomitant use of a P-glycoprotein inhibitor is needed.

Adverse Reactions in IBS-D Trials

Common Adverse Reactions	≥ 2%: ALT increased, nausea
Death/Serious Adverse Events	No deaths occurred. Serious adverse events occurred in 1.5% and 2.2%, and drug-related serious adverse events occurred in 0.1% and 0.2% of rifaximin and placebo groups, respectively. ¹⁵
Discontinuations Due to Adverse Events	No significant difference versus placebo. See Other Safety Considerations .
Comparative Safety / Tolerability	In pooled analyses of Phase II and III trial safety data, the adverse event and tolerability profile of rifaximin was similar to that of placebo. ¹⁵

Other Safety Considerations

Indirect Comparison of Rifaximin and Other Therapies

- In a moderate-quality systematic review / meta-analysis of placebo-controlled trials, the relative risk of withdrawal due to adverse event for rifaximin was not significantly different from that of placebo.⁵
 - The numbers needed to harm (NNH) for withdrawals due to adverse events and numbers needed to treat for benefit (NNT) were
 - 18.3 (95% CI, 5.8–217.4) and 8 (3.7–71.9) for **tricyclic antidepressants** (K = 6, N = 474),
 - 19.4 (8.5–90.1) and 7.5 (4.7–15.8) for **alosetron** (K = 7, N = 4472) and
 - 8971 (6.8–21.5) and 10.6 (6.8–21.5) for **rifaximin** (K = 5, N = 2095).
 - A withdrawal due to adverse event occurred for every 846 IBS-D patients who benefited from rifaximin, and the corresponding number was 2.6 for alosetron and 2.3 for tricyclic antidepressants.
 - The only adverse event with a significantly higher incidence on rifaximin than placebo was bad taste (p = 0.015).

Long-term Studies

- [TARGET 3](#) (51 weeks).

Risk of Clinically Relevant Antibiotic Resistance

- Rifaximin is described as an agent with a low risk of *clinically relevant* antibiotic resistance.
- Mutations generally occur in about 1×10^{-7} to 1×10^{-8} bacteria exposed to high concentrations of rifaximin.²⁰
- Based on analyses of stool samples from a random selection of 100 patients in the TARGET 3 trial, there were no clinically relevant changes in bacterial sensitivity to other antibiotic classes, no microbiota alterations, no development of pathogenic bacteria and no opportunistic infections.¹⁹
- Other studies show that use of rifaximin can lead to the emergence of rifampin resistant staphylococci,²⁹ rifaximin-resistant *E. Coli*,^{30,31} rifaximin-resistant *Bifidobacteria*³² and *Clostridia difficile* resistant to both rifaximin and rifampin.³³
- The risk of developing rifampin-resistant *Mycobacterium tuberculosis* from cross-resistance between rifampin and rifaximin seems to be low.³⁴

Risk of *C. difficile* Colitis

- In IBS-D clinical trials of rifaximin, the incidence of *C. difficile* colitis was zero per 61.3 patient-years of exposure.¹⁵
- The corresponding rates expressed as events per 100 patient-years were 1.7 in Crohn's disease and 1.2 in hepatic encephalopathy trials.¹⁵
- Rifaximin-resistant *C. difficile* isolates have been reported and can be predicted by rifampin resistance.³⁵

Postmarketing Surveillance

- Cases of *C. difficile*-associated colitis and hypersensitivity reactions including exfoliative dermatitis and anaphylaxis have been reported.

Drug Interactions

Drug-Drug

- Rifaximin induction of CYP3A4: suggested in an *in vitro* study but not expected in patients with normal liver function at recommended doses.
- Cyclosporine increases in rifaximin C_{max} by 83-fold and AUC_{inf} by 124-fold in healthy subjects; unknown clinical significance.

Drug-Food

None

Drug-Lab

None

Risk Evaluation

As of 13 January 2016.

Sentinel Event Advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike / Sound-alike Error Potential

The rifaximin / rifampin pair has appeared on the VA cumulative list of look-alike / sound-alike mixups.

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Rifaximin 200mg, 500mg tab	Rifampin	Rifampin Rifamate	Rifampin	Rifapentine Rifabutin Rifater Rifamate
XIFAXAN	None	None	None	XANAX BIAXIN XIAFLEX ZYBAN

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Pharmacokinetic Considerations: IBS-D and healthy subjects showed similar C_{max} and AUC of rifaximin.³⁶ About 97% of the drug is excreted unchanged in the feces.
- Relative Effect Size. According to Menees, et al. (2012), the small effect size (NNT 10) of rifaximin in terms of global IBS response is similar to those reported for other drugs (e.g., tegaserod, lubiprostone, alosetron).¹⁸
- Comparative Actual-Use Effectiveness: No prospective actual-use studies were found.
- Quality of Life (QoL): IBS-related QoL was evaluated at 12 weeks following initiation of a 2-week course of rifaximin in the TARGET 1 and TARGET 2 trials. Rifaximin was significantly better than placebo in improving scores for overall QoL and the subdomains *interference with activity*, *body image*, *social reaction* and *relationships*.³⁷
- A manufacturer-conducted decision-tree economic analysis showed that rifaximin therapy (assuming a median of 3 courses per year at an expected cost of \$6288) as initial treatment for suspected IBS-D would result in an incremental cost savings of \$2,401 relative to initial diagnostic testing (assuming all possible diagnostic tests are performed) followed by treatment.²⁰ The factors with greatest impact on overall expected costs were cost of rifaximin, colonoscopy, gastroenterologist visit, and abdominal / pelvic CT scans.

Dosing and Administration for IBS-D

- One 550 mg tablet 3 times a day for 14 days. Patients who experience recurrence can be retreated up to two times with the same regimen.
- Can be taken with or without food.

Special Populations (Adults)

Elderly	<ul style="list-style-type: none"> In IBS-D trials, 11% of patients were 65 years and older and 2% were 75 years and older. No differences were seen between older and younger study patients. Some older individuals may have greater sensitivity to rifaximin therapy.
Pregnancy	<ul style="list-style-type: none"> No data in pregnant women. Teratogenic in rats and rabbits. Advise pregnant women of the potential risk to the fetus.
Lactation	<ul style="list-style-type: none"> No data in humans. Weigh risks / benefits to mother and infant.
Renal Impairment	<ul style="list-style-type: none"> Not studied.
Hepatic Impairment	<ul style="list-style-type: none"> Systemic exposure (i.e., AUC) increases with increasing degrees of hepatic impairment. No dosage adjustment is recommended because presumably rifaximin acts locally. Use caution when using rifaximin in patients with severe hepatic impairment.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> No data.

Projected Place in Therapy

- IBS Epidemiology. IBS is a common, chronic, complex biopsychosocial gastrointestinal disorder estimated to affect 5% to 15% of the general adult population, with an estimated incidence of new cases of 1% to 2%.^{38,39} In addition to having a substantial negative impact on health-related quality of life, IBS has been associated with suicide, missed work days, and impaired work productivity.³⁹ Relative to non-IBS patients, those with IBS utilize 50% more health care resources, with sequential diagnostic tests, invasive procedures (e.g., colonoscopies) and abdominal operations (e.g., cholecystectomies) accounting for a substantial proportion of health care costs.³⁹ Women are about 1.5 to 2 times more likely to be diagnosed with IBS than men, and patients younger than 50 years of age are more likely than older patients to be affected.^{8,40} The prevalence of IBS was estimated to be 2% to 19% among 1991 Gulf War deployed Veterans,^{41,42} and 3.5% among Operation Enduring Freedom / Operation Iraqi Freedom / Operation New Dawn (OEF / OIF / OND) female Veterans over a 10-year period from FY2002 to FY2012.⁴³ In female Veterans, IBS has been shown to be associated with trauma,⁴⁴ and the odds of having IBS are increased more than 3- to 16-fold in the presence of anxiety, depression or PTSD.⁴⁵ IBS is one of several conditions that overlap with the clinical spectrum of chronic multisystem illness in Veterans.⁴⁶
 - IBS is defined as recurrent abdominal pain or discomfort at least three days per month in the last three months with two or more of the following: onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool or improvement with defecation.
 - IBS-D is a subtype of IBS that represents about 40% of those suffering from IBS and has a prevalence of 5% of the general population.⁴⁷ IBS-D is defined as the presence of loose or watery stools with at least 25 percent of bowel movements and hard or lumpy stools with less than 25 percent of bowel movements (in the absence of laxatives).
 - The pathogenesis of IBS is probably multifactorial, as the disorder is heterogeneous. About one-third of patients with IBS-D show altered rates of fecal bile acid excretion and hepatic bile acid synthesis.^{48,49} The role of SIBO in the etiopathogenesis of IBS has not been established, although there may be substantial overlap between the two conditions depending on the testing method used to diagnose SIBO (in pooled analyses, 54% of patients with a diagnosis of IBS have a positive lactulose or glucose hydrogen breath test for SIBO, whereas 4% of patients with IBS have SIBO based on positive jejunal aspirate and culture).⁵⁰
 - Response to all types of therapies – nonpharmacologic or pharmacologic – is often inadequate. There are no reliable biomarkers that would allow IBS patients to be subgrouped according to underlying physiology or that can be used to assess treatment success, and treatment remains symptom-based. None of the existing therapies relieve all symptoms or change the natural history of IBS. Treatments for IBS-D often relieve diarrhea and urgency but tend to cause constipation and do not relieve pain or other symptoms.
- Place in Therapy Based on Practice Guidelines and Reviews Published in the Past 5 Years:
 - The American Gastroenterology Association (AGA, 2014) gives a conditional recommendation to use rifaximin (over no drug treatment) in patients with IBS-D (moderate quality evidence [QE]).⁵¹ Other treatments were also

given conditional recommendations: alosetron (moderate QE); tricyclic antidepressants (low QE), SSRIs (low QE) and loperamide (very low QE).^a

- UpToDate (2015) suggests that nonabsorbable antibiotics are not for routine use and that they be used for moderate to severe Non-C IBS, particularly when symptoms include bloating, after there is nonresponse to other therapies (i.e., diet low in fermentable oligo-, di-, and monosaccharides and polyols [FODMAP], antispasmodics and TCAs).⁶
- Further studies are needed to determine the risks of *C. difficile* colitis and rifaximin-resistant gut bacteria with repeated courses of rifaximin.
- The evidence of small efficacy for rifaximin in IBS-D / Non-C IBS is moderate in quality and results were consistent across outcome measures and across studies. The evidence of safety is high for short-term treatment and moderate for up to two repeated treatments. The external validity of clinical trial results to the VA population is uncertain; however, there is no compelling reason not to try rifaximin in US Veteran patients.
- Rifaximin is the third agent approved for IBS-D and the second treatment approved without restrictions related to gender, IBS severity or prescription-program dispensing. Although rifaximin has been described as an antibiotic with a low likelihood of resistance,^{17,20} the risk of developing bacterial resistance with long-term or repeated treatment with rifaximin remains an important concern that may outweigh the relatively small benefits provided by rifaximin therapy in IBS-D. The cost of rifaximin also weighs against the frequent use of rifaximin for IBS. Rifaximin for IBS should be restricted to patients who have the IBS-D subtype and have not responded to effective and less costly symptom-based alternative therapies. Use of rifaximin should be limited to 3 courses of treatment (the initial and, if there is recurrence, up to two repeat treatments).

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^a **Conditional recommendation:** Patients: the majority of people in this situation would want the suggested course of action, but many may not. Decision aids are useful in helping individuals make decisions consistent with their values and preferences. Clinicians: examined a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making). Policy makers: there is a need for substantial debate and involvement of stakeholders.

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 patients; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.