

## Xifaxan (rifaximin) 550 mg Tablets

### Disclaimer

*Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.*

*Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.*

Xifaxan (rifaximin) 550 mg Tablets	1
Summary	1
Definitions	2
Clinical Indications	2
Medical Necessity Criteria for Initial Clinical Review	2
Initial Indication-Specific Criteria	2
Hepatic Encephalopathy, Treatment or Prevention:	2
For the treatment of Irritable Bowel Syndrome with diarrhea:	3
For the treatment of Small Intestinal Bacterial Overgrowth (SIBO):	3
Medical Necessity Criteria for Subsequent Clinical Review	4
Subsequent Indication-Specific Criteria	4
Hepatic Encephalopathy, Treatment or Prevention	4
For the treatment of Irritable Bowel Syndrome with diarrhea:	4
For the treatment of Small Intestinal Bacterial Overgrowth (SIBO):	4
Experimental or Investigational / Not Medically Necessary[s]	5
References	5
Clinical Guideline Revision / History Information	7

## Summary

Xifaxan (rifaximin) is an antibiotic that primarily targets the gastrointestinal tract, available in two formulation strengths - 200 mg tablets and 550 mg tablets. It inhibits bacterial and mycobacterial RNA synthesis, thereby disrupting protein production in these microorganisms. Rifaximin is FDA indicated for use in hepatic encephalopathy, irritable bowel syndrome with diarrhea, and traveler's diarrhea, as well as for off-label use in small intestinal bacterial overgrowth (SIBO). Given its minimal absorption in the gastrointestinal tract, its effects remain largely localized. The 200 mg formulation is used for treatment of traveler's diarrhea while the 550 mg formulation is intended for the treatment of hepatic encephalopathy, irritable bowel syndrome with diarrhea, and SIBO. The 550 mg dosage form is also used for the off-label use of acute, refractory pouchitis. The most common adverse reactions associated with rifaximin include abdominal pain and nausea.

This policy covers only the 550 mg tablet dosage form on Xifaxan (rifaximin).

### Definitions

"Hepatic encephalopathy" is a decline in brain function that occurs as a result of severe liver disease. This is often due to an accumulation of toxins, such as ammonia, which are not effectively cleared by a damaged liver.

"Irritable bowel syndrome" is a chronic functional disorder of the gastrointestinal tract characterized by a combination of symptoms including chronic abdominal pain, bloating, and changes in bowel habits in the absence of any visible damage or disease.

"Small Intestinal Bacterial Overgrowth (SIBO)" is a condition characterized by an abnormal increase in the overall bacterial population in the small intestine, particularly types of bacteria not typically found in that part of the digestive tract.

"Traveler's diarrhea" is an intestinal infection that commonly causes loose stools and abdominal cramps. It's usually acquired during travel to areas with poor sanitary conditions affecting food and water.

"[s]" indicates state mandates may apply.

## Clinical Indications

### Medical Necessity Criteria for Initial Clinical Review

#### Initial Indication-Specific Criteria

##### Hepatic Encephalopathy, Treatment or Prevention:

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL the following criteria are met:

1. The member is age 18 years or older; *AND*
2. The member has a diagnosis of hepatic encephalopathy; *AND*
3. Xifaxan (rifaximin) 550mg is being prescribed for ONE (1) of the following:
  - a. to be added to lactulose therapy; *or*
  - b. the member is unable to use, or has tried and failed lactulose (i.e., the member has intolerable side effects, ineffectiveness after a specified duration, or specific worsening symptoms with lactulose)<sup>[s]</sup>.

If the above prior authorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for 6 months.<sup>[s]</sup>

##### For the treatment of Irritable Bowel Syndrome with diarrhea:

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL the following criteria are met:

1. The member is age 18 years or older; *AND*
2. The member has a diagnosis of irritable bowel syndrome with diarrhea; *AND*
3. The member is unable to use, or has tried and failed TWO (2) of the following, each from a different drug class<sup>[s]</sup>:
  - a. Antispasmodic agents (such as dicyclomine, hyoscyamine); *or*
  - b. Antidiarrheal agents (such as loperamide); *or*
  - c. Tricyclic antidepressants (such as amitriptyline, nortriptyline, imipramine)

If the above prior authorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for 14 days.<sup>[s]</sup>

##### For the treatment of Small Intestinal Bacterial Overgrowth (SIBO):

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL the following criteria are met:

1. The member has a diagnosis of small intestinal bacterial overgrowth, confirmed through a breath test or other appropriate diagnostic methods; *AND*
2. The member is unable to use, or has tried and failed ONE (1) of the following<sup>[s]</sup>:
  - a. Amoxicillin/Clavulanic Acid; *or*
  - b. Ciprofloxacin; *or*

- c. Doxycycline; *or*
- d. Metronidazole; *or*
- e. Neomycin; *or*
- f. Sulfamethoxazole/Trimethoprim; *or*
- g. Tetracycline

If the above prior authorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for 14 days.<sup>[s]</sup>

#### *Continued Care*

#### Medical Necessity Criteria for Subsequent Clinical Review

##### Subsequent Indication-Specific Criteria

##### Hepatic Encephalopathy, Treatment or Prevention

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL of the following criteria are met:

1. The member meets the above [Initial Indication-Specific Criteria - Hepatic Encephalopathy, Treatment or Prevention](#); *AND*
2. There is documentation showing positive clinical benefit, improvement (such as reduction in the severity/frequency of hepatic encephalopathy episodes), or stabilization of hepatic encephalopathy symptoms with Xifaxan (rifaximin) therapy.

If the above reauthorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for up to 6-months.<sup>[s]</sup>

##### For the treatment of Irritable Bowel Syndrome with diarrhea:

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL of the following criteria are met:

1. The member is age 18 years or older; *AND*
2. The member has a diagnosis of irritable bowel syndrome with diarrhea; *AND*
3. The member is experiencing a recurrence of symptoms; *AND*
4. The member has not received more than 3 total treatment cycles of 14 days each in the last 365 days.

If the above reauthorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for up to 14 days at a time (up to 3 total treatment cycles per year).<sup>[s]</sup>

#### For the treatment of Small Intestinal Bacterial Overgrowth (SIBO):

The Plan considers Xifaxan (rifaximin) 550mg medically necessary when ALL of the following criteria are met:

1. The member has a diagnosis of small intestinal bacterial overgrowth; *AND*
2. The member is experiencing a recurrence of symptoms; *AND*
3. The member has not received more than 2 total treatment cycles of 14 days each in the last 90 days.

If the above reauthorization criteria are met, Xifaxan (rifaximin) 550mg will be approved for 14 days at a time (up to 2 total treatment cycles).<sup>[s]</sup>

#### Experimental or Investigational / Not Medically Necessary<sup>[s]</sup>

Xifaxan (rifaximin) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

#### References

1. American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014 Sep;61(3):642-59. doi: 10.1016/j.jhep.2014.05.042. Epub 2014 Jul 8. Erratum in: J Hepatol. 2015 Oct;63(4):1055.
2. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009; 104 Suppl 1:S1.
3. Aspinall RJ, Hudson M, Ryder SD, et al. Real-world evidence of long-term survival and healthcare resource use in patients with hepatic encephalopathy receiving rifaximin- $\alpha$  treatment: a retrospective observational extension study with long-term follow-up (IMPRESS II). Frontline Gastroenterol. 2022 Nov 10;14(3):228-235. doi: 10.1136/flgastro-2022-102221. Erratum in: Frontline Gastroenterol. 2023 Dec 7;15(1):e1. doi: 10.1136/flgastro-2022-102221corr1.
4. Bajaj JS, Barrett AC, Bortey E, et al. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. Aliment Pharmacol Ther 2015; 41:39.
5. Barnes EL, Agrawal M, Syal G, Ananthakrishnan AN, Cohen BL, Haydek JP, Al Kazzi ES, Eisenstein S, Hashash JG, Sultan SS, Raffals LE, Singh S; AGA Clinical Guidelines Committee. Electronic address: clinicalpractice@gastro.org. AGA Clinical Practice Guideline on the Management of Pouchitis and Inflammatory Pouch Disorders. Gastroenterology. 2024 Jan;166(1):59-85. doi: 10.1053/j.gastro.2023.10.015. PMID: 38128971; PMCID: PMC11163976.
6. Barnes EL, Agrawal M, Syal G, Ananthakrishnan AN, Cohen BL, Haydek JP, Al Kazzi ES, Eisenstein S, Hashash JG, Sultan SS, Raffals LE, Singh S; AGA Clinical Guidelines Committee. Electronic address: clinicalpractice@gastro.org. AGA Clinical Practice Guideline on the Management of Pouchitis and Inflammatory Pouch Disorders. Gastroenterology. 2024 Jan;166(1):59-85. doi: 10.1053/j.gastro.2023.10.015. PMID: 38128971; PMCID: PMC11163976.
7. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010 Mar 25;362(12):1071-81. doi: 10.1056/NEJMoa0907893.

8. Black CJ, Ford AC. Best management of irritable bowel syndrome. *Frontline Gastroenterol*. 2020 May 28;12(4):303-315. doi: 10.1136/flgastro-2019-101298.
9. Calanni, F., Renzulli, C., Barbanti, M., & Viscomi, G. C. (2014). Rifaximin: beyond the traditional antibiotic activity. *The Journal of antibiotics*, 67(9), 667-670.
10. Chang L et al: AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with constipation. *Gastroenterology*. 163(1):118-36, 2022.
11. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022 Sep;77(3):807-824. doi: 10.1016/j.jhep.2022.06.001. Epub 2022 Jun 17. Erratum in: *J Hepatol*. 2023 Nov;79(5):1340. doi: 10.1016/j.jhep.2023.09.004.
12. Flamm SL. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. *Therap Adv Gastroenterol*. 2011 May;4(3):199-206. doi: 10.1177/1756283X11401774.
13. Hanna-Jairala I, Drossman DA. Central Neuromodulators in Irritable Bowel Syndrome: Why, How, and When. *Am J Gastroenterol*. 2024 Jul 1;119(7):1272-1284. doi: 10.14309/ajg.0000000000002800. Epub 2024 Apr 9.
14. Isaacs KL, Sandler RS, Abreu M, Picco MF, Hanauer SB, Bickston SJ, Present D, Farraye FA, Wolf D, Sandborn WJ; Crohn's and Colitis Foundation of America Clinical Alliance. Rifaximin for the treatment of active pouchitis: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2007 Oct;13(10):1250-5. doi: 10.1002/ibd.20187. PMID: 17567869.
15. Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, Wilcox MH. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults. *Clin Infect Dis*. 2021 Sep 7;73(5):e1029-e1044. doi: 10.1093/cid/ciab549. PMID: 34164674.
16. Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, Stollman NH. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. *Am J Gastroenterol*. 2021 Jun 1;116(6):1124-1147. doi: 10.14309/ajg.0000000000001278. Erratum in: *Am J Gastroenterol*. 2022 Feb 1;117(2):358. doi: 10.14309/ajg.0000000000001529. PMID: 34003176.
17. Koo, H. L., & DuPont, H. L. (2010). Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Current opinion in gastroenterology*, 26(1), 17.
18. Lembo A et al: AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*. 163(1):137-51, 2022
19. Mearin F et al: Clinical practice guideline: irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig*. 108(6):332-63, 2016
20. Moayyedi P et al: Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome (IBS). *J Can Assoc Gastroenterol*. 2(1):6-29, 2019.
21. Moon AM, Kim HP, Jiang Y, et al. Systematic Review and Meta-Analysis on the Effects of Lactulose and Rifaximin on Patient-Reported Outcomes in Hepatic Encephalopathy. *Am J Gastroenterol*. 2023 Feb 1;118(2):284-293. doi: 10.14309/ajg.0000000000002008. Epub 2022 Aug 22.
22. Pimentel M, Saad R, Long M, et al. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *Am J Gastroenterol* 2020; 115:165.
23. Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. *Infect Dis Clin North Am* 2010; 24:943.
24. Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011; 34:853.
25. Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2013; 38:925.
26. Shen B, Kochhar GS, Rubin DT, Kane SV, Navaneethan U, Bernstein CN, Cross RK, Sugita A, Schairer J, Kiran RP, Fleshner P, McCormick JT, D'Hoore A, Shah SA, Farraye FA, Kariv R, Liu X, Rosh J, Chang S, Scherl E, Schwartz DA, Kotze PG, Bruining DH, Philpott J, Abraham B, Segal J, Sedano R, Kayal M, Bentley-Hibbert S, Tarabar D, El-Hachem S, Sehgal P, Picoraro JA, Vermeire

- S, Sandborn WJ, Silverberg MS, Pardi DS. Treatment of pouchitis, Crohn's disease, cuffitis, and other inflammatory disorders of the pouch: consensus guidelines from the International Ileal Pouch Consortium. *Lancet Gastroenterol Hepatol*. 2022 Jan;7(1):69-95. doi: 10.1016/S2468-1253(21)00214-4. Epub 2021 Nov 10. PMID: 34774224.
27. Steffen R, Sack DA, Riopel L, et al. Therapy of travelers' diarrhea with rifaximin on various continents. *Am J Gastroenterol* 2003; 98:1073.
28. Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut*. 2021 Jul;70(7):1214-1240. doi: 10.1136/gutjnl-2021-324598. Epub 2021 Apr 26.
29. Xifaxan (rifaximin) [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals Inc; October 2023.

#### Clinical Guideline Revision / History Information

Original Date: 08/06/2020

Reviewed/Revised: 06/24/2021, 12/01/2021, 06/23/2022, 06/29/2023, 10/27/2023, 12/19/2024, 10/01/2025, 03/02/2026