Drug Coverage Policy

Effective Date.....1/1/2025
Coverage Policy Number.....IP0473
Policy Title.....Xifaxan

Antibiotics – Xifaxan for Individual and Family Plans

Xifaxan® (rifaximin tablets – Salix)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Xifaxan, a rifamycin antibiotic, is indicated for the following uses:[1]

- ***Hepatic encephalopathy (HE)**, to reduce the risk of overt disease in adults.*
- ***Irritable bowel syndrome with diarrhea (IBS-D)**, in adults.*
- ***Travelers' diarrhea (TD)**, caused by noninvasive Escherichia coli in patients ≥ 12 years of age.*

Limitations of Use: TD: Xifaxan should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.[1]

In the trials of Xifaxan for HE, 91% of the patients were using lactulose concomitantly.[1] Due to small sample size, differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed. Data are lacking to support the use of Xifaxan without concomitant use of lactulose.

Guidelines

- **Hepatic Encephalopathy**: The European Association for the Study of the Liver (EASL) guidelines for HE (2022) recommend Xifaxan as an adjunct to lactulose as secondary prophylaxis following ≥ 1 additional episode of overt HE within 6 months of the first episode.[2] Guidelines also state that in patients with cirrhosis and previous episodes of overt HE, Xifaxan can be considered for prophylaxis of HE prior to non-urgent transjugular intrahepatic portosystemic shunt (TIPS) placement.
- **IBS with Diarrhea**: The American College of Gastroenterology (ACG) guidelines for the management of IBS (2021) suggest Xifaxan to reduce the global symptoms of IBS and to reduce bloating in non-constipated IBS patients.[3] In addition, the American Gastroenterological Association (AGA) guidelines on the management of IBS-D (2022) suggest Xifaxan over no drug treatment for patients with IBS-D (conditional recommendation, moderate evidence).[4]
- **Small Intestine Bacterial Overgrowth (SIBO):** Clinical guidelines from the ACG (2020) and the AGA (2020) list Xifaxan as an option for the treatment of SIBO.[9,10] ACG also states that the diagnosis of SIBO can be made with breath testing (glucose hydrogen or lactulose hydrogen), or by small bowel aspiration and culture. Of note, in clinical trials, patients were treated with Xifaxan for a 7-day course for SIBO.[5-8]
- **Travelers' Diarrhea**: The Centers for Disease Control and Prevention Yellow Book – Health Information for International Travel (2024) states that Xifaxan may be used for the treatment of moderate, noninvasive travelers' diarrhea and may be used for the treatment of severe, non-dysenteric travelers' diarrhea.[11] In addition, guidelines developed by an expert panel (2017) state that Xifaxan is appropriate for moderate or severe, non-dysenteric travelers' diarrhea, and when indicated for the prophylaxis of travelers' diarrhea.[12]

Medical Necessity Criteria

Xifaxan is considered medically necessary when ONE of the following are met:

FDA-Approved Indications

1. **Hepatic Encephalopathy.** Approve Xifaxan 550 mg tablets for 6 months if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** According to the prescriber, the patient has previously had overt hepatic encephalopathy; AND
   - **C)** Patient meets ONE of the following criteria (i or ii):
     - **i.** Xifaxan will be used concomitantly with lactulose; OR
     - **ii.** According to the prescriber, the patient has a contraindication or significant intolerance to treatment with lactulose.

2. **Irritable Bowel Syndrome with Diarrhea.** Approve Xifaxan 550 mg tablets for 14 days if the patient is ≥ 18 years of age.

3. **Travelers' Diarrhea**. Approve Xifaxan 200 mg tablets for 3 days if the patient meets ALL of the following (A, B, C and D):
   A) Patient is ≥ 12 years of age; AND
   B) According to the prescriber, the patient is afebrile; AND
   C) According to the prescriber, the patient does not have blood in the stool.
   D) Preferred product criteria is met for the product(s) as listed in the below table.

Individual and Family Plans:

Product	Criteria
Xifaxan 200 mg (rifaximin tablets)	Traveler's Diarrhea. **ONE** of the following: 1. Currently receiving Xifaxan 200 mg tablets in order to complete course of therapy. 2. Failure, contraindication, or intolerance to **ONE** of the following: A. azithromycin B. ciprofloxacin C. levofloxacin D. ofloxacin

Other Uses with Supportive Evidence

4. **Small Intestine Bacterial Overgrowth.** Approve Xifaxan (either strength) for 14 days if small intestine bacterial overgrowth is diagnosed by ONE of the following (A, B, or C):
   A) Glucose hydrogen breath test; OR
   B) Lactulose hydrogen breath test; OR
   C) Small bowel aspiration and culture.

5. **Pouchitis, Chronic Antibiotic-Dependent**. Approve Xifaxan (either strength) for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient has recurrent pouchitis; AND
   Note: Recurrent pouchitis is typically considered a history of ≥ 3 pouchitis episodes within a 12 month period.
   B) According to the prescriber, the episodes of pouchitis respond to antibiotic therapy but relapse shortly after antibiotic discontinuation; AND
   C) According to the prescriber, alternative causes of recurrent pouchitis have been ruled out; AND
   Note: Alternative etiologies of recurrent pouchitis include but are not limited to *Clostridioides difficile* infection of the pouch, mechanical obstructions, pelvic floor dysfunction.
   D) Patient has tried long-term antibiotic therapy trials (at least 4 weeks) of BOTH ciprofloxacin and metronidazole for remission maintenance; AND
   E) The medication is prescribed by, or in consultation with, a gastroenterologist.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. ***Helicobacter pylori* Infection**. The ACG guidelines for the treatment of *H. pylori* do not address the use of Xifaxan.[13] There are limited trials assessing the efficacy of Xifaxan in the treatment of *H. pylori* infection in adults; the available studies are small, of poor quality, and not conducted in the United States. More data are needed to define the place in therapy of rifaximin in the treatment of *H. pylori*.

References

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4. Lembo A, Sultan S, et al. American Gastroenterological Association AGA clinical practice guideline on the pharmacological management of irritable bowel syndrome with diarrhea. *Gastroenterology*. 2022;163:137-151.
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8. Scarpellini E, Giorgio V, Gabrielli M, et al. Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome: A preliminary study. *Eur Rev Med Pharmacol Sci*. 2013;17:1314-1320.
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10. Quigley EMM, Murray JA, Pimental M. AGA Clinical Practice update on small intestinal bacterial overgrowth: Expert review. *Gastroenterology*. 2020;159:1526-1532.
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13. Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: Treatment of Helicobacter pylori infection. *Am J Gastroenterol*. 2017;112:212-238.
14. Barnes EL, Agrawal M, Syal G, et al. AGA Clinical Practice Guideline on the Management of Pouchitis and Inflammatory Pouch Disorders. Gastroenterology. 2024;166(1):59-85.

Revision Details

Type of Revision	Summary of Changes	Date

Annual Revision	**Updated** policy title from "Rifaximin for Individual and Family Plans" to "Antibiotics – Xifaxan for Individual and Family Plans". **<u>Traveler's Diarrhea.</u>** **Added** criterion screening the patient is afebrile. **Added** criterion screening the patient does not have blood in stool. **<u>Pouchitis, Chronic Antibiotic-Dependent.</u>** **Updated** format of recurrent pouchitis criterion **Added** "According to the prescriber, the episodes of pouchitis respond to antibiotic therapy but relapse shortly after antibiotic discontinuation". **Added** "According to the prescriber, alternative causes of recurrent pouchitis have been ruled out; AND Note: Alternative etiologies of recurrent pouchitis include but are not limited to Clostridioides difficile infection of the pouch, mechanical obstructions, pelvic floor dysfunction". **Added** "The medication is prescribed by, or in consultation with, a gastroenterologist".	7/1/2024

The policy effective date is in force until updated or retired.