Effective Date **6/1/2023**
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Coverage Policy Number **IP0473**

Rifaximin for Individual and Family Plans

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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. 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.

Overview

This policy supports medical necessity review for the following rifaximin products for Individual and Family Plans:

- **Xifaxan® 200 mg** tablets
- **Xifaxan® 550 mg** tablets

Additional criteria that support the review for medical necessity exceptions of non-covered products are located in the Non-Covered Product Table by the respective plan type and drug list where applicable.

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

Medical Necessity Criteria

Rifaximin products (Xifaxan) are considered medically necessary when the following are met:

I. **Xifaxan 200 mg tablets.** Individual meets **ONE** of the following:

1. **Travelers' Diarrhea.** Individual meets **BOTH** of the following criteria:
    A. 12 years of age or older
    B. Non-Covered Product Criteria is met, refer to table below:

Individual and Family Plan Non-Covered Products and Covered Alternative(s):

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

2. **Chronic Antibiotic-dependent Pouchitis (CADP).** Individual meets **BOTH** of the following criteria:
    A. Diagnosis of chronic antibiotic-dependent pouchitis (for example, 3 or more episodes per year treated with ciprofloxacin, metronidazole, tindiazole, or combination therapy)
    B. The episodes of pouchitis required long-term (at least 4 weeks) therapy for remission maintenance

3. **Small Intestine Bacterial Overgrowth.** Individual meets the following criteria:
    A. Intestine bacterial overgrowth is diagnosed by **ONE** of the following criteria:
        i. Glucose hydrogen breath test
        ii. Lactulose hydrogen breath test
        iii. Small bowel aspiration and culture

II. **Xifaxan 550 mg tablets.** Individual meets **ONE** of the following:

1. **Chronic Antibiotic-dependent Pouchitis (CADP).** Individual meets **BOTH** of the following criteria:
    A. Diagnosis of chronic antibiotic-dependent pouchitis (for example, 3 or more episodes per year treated with ciprofloxacin, metronidazole, tindiazole, or combination therapy)
    B. The episodes of pouchitis required long-term (at least 4 weeks) therapy for remission maintenance

2. **Hepatic Encephalopathy.** Individual meets **ALL** of the following criteria:
    A. 18 years of age or older
    B. Previously had hepatic encephalopathy
    C. **ONE** of the following criteria:
        i. Xifaxan will be used concomitantly with lactulose
        ii. Contraindication or significant intolerance to treatment with lactulose

3. **Irritable Bowel Syndrome with Diarrhea.** Individual meets the following criteria:
    A. 18 years of age or older

4. **Small Intestine Bacterial Overgrowth.** Individual meets the following criteria:
    A. Intestine bacterial overgrowth is diagnosed by **ONE** of the following criteria:
        i. Glucose hydrogen breath test
        ii. Lactulose hydrogen breath test
        iii. Small bowel aspiration and culture

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.

Reauthorization Criteria

Rifaximin (Xifaxan) is considered medically necessary for continued use when **ONE** of the following is met:

1. **Chronic Antibiotic-dependent Pouchitis (CADP).** Individual meets the following criteria:
    A. Initial criteria are met AND there is documentation of beneficial response

2. **Hepatic Encephalopathy.** Individual meets the following criteria:
    A. Initial criteria are met AND there is documentation of beneficial response

3. **Irritable Bowel Syndrome with Diarrhea.** Individual meets **BOTH** the following criteria:
    A. Initial criteria are met
    B. Receiving Xifaxan for 14 days for repeat treatment, up to a total of 2 repeat treatment courses within 6 months.

4. **Small Intestine Bacterial Overgrowth.** Individual meets the following criteria:
    A. Initial criteria are met
    B. Receiving Xifaxan for 14 days for repeat treatment, up to a total of 2 repeat treatment courses within 6 months

Authorization Duration

Xifaxan 200 mg tablets

Initial approval duration:

- **Travelers' Diarrhea:** up to 3 days
- **Small Intestine Bacterial Overgrowth:** up to 2 weeks
- **Chronic Antibiotic-dependent Pouchitis (CADP):** up to 6 months

Reauthorization approval duration:

- **Travelers' Diarrhea:** Not applicable
- **Small Intestine Bacterial Overgrowth:** three 14 day courses over 6 months
- **Chronic Antibiotic-dependent Pouchitis (CADP):** up to 12 months

Xifaxan 550 mg tablets

Initial approval duration:

- **Hepatic Encephalopathy:** up to 6 months
- **Irritable Bowel Syndrome with Diarrhea:** up to 2 weeks
- **Small Intestine Bacterial Overgrowth:** up to 2 weeks
- **Chronic Antibiotic-dependent Pouchitis (CADP**): up to 6 months

Reauthorization approval duration:

- **Hepatic Encephalopathy:** up to 12 months
- **Irritable Bowel Syndrome with Diarrhea:** three 14 day courses over 6 months
- **Small Intestine Bacterial Overgrowth:** three 14 day courses over 6 months
- **Chronic Antibiotic-dependent Pouchitis (CADP):** up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

***Helicobacter pylori* Infection**. There are limited data assessing the efficacy of Xifaxan in the treatment of *H. pylori* infection in adults.[7-9] The available studies are small, of poor quality, and none of the studies were conducted in the United States. In addition, ACG treatment guidelines do not address the use of Xifaxan for the treatment of *H. pylori*.

Background

OVERVIEW

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

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

In the trials of Xifaxan for hepatic encephalopathy, 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.

Limitations of Use: 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]

Guidelines

- **Hepatic Encephalopathy**: The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) developed practice guidelines for the management of hepatic encephalopathy (2014).[6] The AASLD/EASL guidelines state that Xifaxan add-on to lactulose is effective for the prevention of overt hepatic encephalopathy and for the prevention of recurrent episodes of hepatic encephalopathy after the second episode.
- **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.[7] In addition, the American Gastroenterological Association (AGA) guidelines on the management of IBS (2014) suggest Xifaxan over no drug treatment for patients with IBS with diarrhea.[8]
- **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.[2-5]
- **Travelers' Diarrhea**: The Centers for Disease Control and Prevention Yellow Book – Health Information for International Travel (2020) 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]

Additional Clinical Information

- **Chronic Antibiotic-dependent Pouchitis (CADP).** Pouchitis is the most common complication in patients who have undergone restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA).[13] First-line therapy for acute pouchitis includes ciprofloxacin 500mg twide daily or metronidazole 500mg three times a day for 2–4 weeks. After initial treatment for pouchitis, approximately 60% of patients will develop at least one recurrence and up to 20% will develop chronic pouchitis.[13] Long-term maintenance with antibiotics may be required. Rifaximin has been shown to be effective as maintenance monotherapy

in CADP at doses of 200 mg daily with the opportunity to increase up to 1800 mg per day for patients who exhibited at least partial response to the initial dose.[13] The majority of these patients were responsive to 200 mg daily.[14] Rifaximin has also been shown to be effective in a small study using rifaximin 1 g BID in combination with ciprofloxacin 500 mg BID for use in CADP.[15]

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