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Section:	Prescription Drugs	**Effective Date:**	July 1, 2024
Subsection:	Anti-Infective Agents	**Original Policy Date:**	July 24, 2015
Subject:	Xifaxan	**Page:**	1 of 7

Last Review Date: June 13, 2024

Xifaxan

Description

Xifaxan (rifaximin)

Background
Xifaxan is a semi-synthetic antibacterial derived from rifampin. Xifaxan is used for the treatment of traveler's diarrhea (TD) caused by *Escherichia coli* (E.coli), for the reduction of the risk of recurring overt hepatic encephalopathy (HE), and for the treatment of irritable bowel syndrome with diarrhea (IBS-D) characterized by pain or discomfort in the abdomen and loose or watery stools. While an off-label use, Xifaxan is considered the standard of care in the treatment of small intestinal bacterial overgrowth, as studies have shown its superior efficacy and side effect profile when compared to alternatives. Xifaxan acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase blocking one of the steps in transcription. This results in inhibition of bacterial protein synthesis and consequently inhibits the growth of bacteria (1-3).

Regulatory Status
FDA-approved indications: Xifaxan is a rifamycin antibacterial indicated for: (1)

1. Treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adults and pediatric patients 12 years of age and older.
2. Reduction in the risk of overt hepatic encephalopathy recurrence in adults
3. Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults

Limitation 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 *Escherichia coli* (1).

Off-Label Uses:

1. Small intestinal bacterial overgrowth (SIBO) - Xifaxan has been studied in adults 18 years of age or older for the off-label use for treatment of small intestinal bacterial overgrowth at a dose of one 550 mg tablet taken orally three times per day for 14 days (2-4)
2. Prevention of Traveler's Diarrhea (TD) – Xifaxan has been studied in adults 18 years of age or older for the off-label use for treatment of prevention of traveler's diarrhea at a dose of one 200 mg tablet taken up to three times per day for 14 days (5)

Xifaxan is contraindicated in people with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components of Xifaxan (1).

Xifaxan was not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. Discontinue Xifaxan if diarrhea symptoms get worse or persist more than 24 to 48 hours and alternative antibiotic therapy should be considered. Xifaxan has been associated with *Clostridium difficile*-associated diarrhea (CDAD) and may range in severity from mild diarrhea to fatal colitis (1).

Xifaxan dosage for irritable bowel syndrome with diarrhea is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen (1).

The safety and effectiveness of Xifaxan have not been established in pediatric patients less than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D (1).

Related policies
Aemcolo, Viberzi

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Xifaxan may be considered **medically necessary** if the conditions indicated below are met.

Xifaxan may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Traveler's diarrhea caused by noninvasive strains of *Escherichia coli*
    a. 12 years of age or older
    b. **NO** dual therapy with another Prior Authorization (PA) medication for Travelers' diarrhea (see Appendix 1)

2. Prevention of Traveler's diarrhea
    a. 18 years of age or older

3. Hepatic encephalopathy
    a. 18 years of age or older

4. Irritable bowel syndrome with diarrhea (IBS-D)
    a. 18 years of age or older
    b. Inadequate treatment response to dietary modification (such as low carbohydrate diet, exclusion of gas producing foods, lactose free diet if intolerant)
    c. Inadequate treatment response, intolerance, or contraindication to **TWO** anti-diarrheal medications

5. Small intestinal bacterial overgrowth (SIBO)
    a. 18 years of age or older
    b. Inadequate treatment response to dietary modification (such as low carbohydrate diet, exclusion of gas producing foods, lactose free diet if intolerant)
    c. Inadequate treatment response, intolerance, or contraindication to another antibiotic for SIBO (e.g., amoxicillin-clavulanic acid, ciprofloxacin, metronidazole, etc.)

Prior – Approval *Renewal* Requirements

Same as above

Policy Guidelines

Pre - PA Allowance

Age 12 years of age or older
Quantity 200 mg – 18 tablets per 365 days
550 mg – 42 tablets per 365 days

Prior - Approval Limits

Quantity **Traveler's Diarrhea**
200 mg – 9 tablets per 90 days
Duration 3 months

Quantity **Hepatic Encephalopathy**
550 mg – 180 tablets per 90 days
Duration 12 months

Quantity **Irritable Bowel Syndrome with Diarrhea (IBS-D) OR Small Intestinal Bacterial Overgrowth (SIBO)**
550 mg – 126 tablets per **365 days**

Quantity **Prevention of Travelers' Diarrhea**
200 mg – 28 tablets per 90 days
Duration 3 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Xifaxan is a semi-synthetic antibacterial derived from rifampin indicated for use in patients 12 years of age and older with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* and in patients 18 years of age and older for the reduction in risk of overt hepatic encephalopathy recurrence and the treatment of irritable bowel syndrome with diarrhea or small

intestinal bacterial overgrowth (SIBO). There are no adequate and well-controlled studies to document the safety and efficacy of Xifaxan in children (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Xifaxan while maintaining optimal therapeutic outcomes.

References

1. Xifaxan [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, Inc.; October 2023.
2. Lauritano EC, Gabriello M, Scarpellini E, et al. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci.* 2009 Mar-Apr;13(2):111-6.
3. Scarpellini E, Gabrielli M, Lauritano CE, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2007; 25:781.
4. Pimentel M, Sadd, RJ, Long MD, et al. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *Am J Gastroenterol.* 2020;115(2):165-78.
5. DuPont, H.L., Z.D. Jiang, et al.. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* 2005; 142: 805-812.

Policy History

Date	Action
July 2015	New addition to PA
September 2015	Annual review
December 2015	Annual review
March 2016	Annual review Removal of renewal for irritable bowel syndrome Policy code changed from 5.03.34 to 5.01.34
September 2016	Match initiation to renewal and add renewal limits for IBS-D
December 2016	Annual review
December 2017	Annual editorial review and reference update Change of duration for Hepatic Encephalopathy from 3 months to 12 months Addition of Small intestinal bacterial overgrowth (SIBO)
November 2018	Annual review and reference update
January 2019	Addition of no dual therapy with another PA Travelers' diarrhea medication to TD requirements

March 2019	Annual review. Added Pre-PA allowance for 550 mg tablets and increased Pre-PA allowance for 200 mg tablets to 18 tablets per 365 days. Added indication of Prevention of Traveler's diarrhea per SME
December 2020	Annual review and reference update
December 2021	Annual editorial review and reference update. Changed t/f requirement for SIBO from "t/f two anti-diarrheals" to "t/f another antibiotic for SIBO"
September 2022	Annual review
January 2023	Added examples of antibiotics for SIBO (e.g., amoxicillin-clavulanic acid, ciprofloxacin, metronidazole, etc.)
March 2023	Annual review
June 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 13, 2024 and is effective on July 1, 2024.

Appendix 1 - List of PA Travelers' Diarrhea Medications

Generic Name	Brand Name
rifamycin	Aemcolo
rifaximin	Xifaxan