Clinical Policy: Rifaximin (Xifaxan)

Reference Number: ERX.NPA.40
Effective Date: 06.01.15
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Rifaximin (Xifaxan®) is an oral rifamycin antibacterial.

FDA Approved Indication(s)
Xifaxan is indicated for the:
- Treatment of travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults

Limitation(s) of use in TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Xifaxan is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hepatic Encephalopathy (must meet all)**:**
1. Diagnosis of HE;
2. Age ≥ 18 years;
3. Failure of lactulose monotherapy in the past 30 days at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Xifaxan is prescribed concurrently with lactulose, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 1,100 mg (2 tablets) per day.

Approval duration: 6 months

B. Irritable Bowel Syndrome with Diarrhea (must meet all)**:**
1. Diagnosis of IBS-D;
2. Age ≥ 18 years;
3. Failure of an anti-diarrheal agent (e.g., loperamide) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of an antispasmodic agent (e.g., dicyclomine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 1,650 mg (3 tablets) per day.

Approval duration: 14 days

C. Travelers' Diarrhea (must meet all)**:**
1. Diagnosis of TD;

2. Age ≥ 12 years;
3. Failure of azithromycin 1,000 mg as a single dose, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 600 mg (3 tablets) per day.

Approval duration: 3 days

D. Small Intestinal Bacterial Overgrowth (off-label) (must meet all)**:**
1. Diagnosis of small intestinal bacterial overgrowth (SIBO);
2. Age ≥ 12 years;
3. Dose does not exceed 1,650 mg (3 tablets) per day.

Approval duration: Up to 14 days

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Hepatic Encephalopathy (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Xifaxan is prescribed concurrently with lactulose, unless contraindicated or clinically significant adverse effects are experienced;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 1,100 mg (2 tablets) per day.

Approval duration: 12 months

B. Irritable Bowel Syndrome with Diarrhea (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member has not had ≥ three 14-day treatment courses that started within the last 6 months;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 1,650 mg (3 tablets) per day.

Approval duration: 14 days

C. Travelers' Diarrhea
1. Re-authorization is not permitted. Members must meet the initial approval criteria. Review initial approval criteria for new cases of travelers' diarrhea unrelated to original medication request.

Approval duration: Not applicable

D. Small Intestinal Bacterial Overgrowth (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 1,650 mg (3 tablets) per day.

Approval duration: Up to 14 days

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
HE: hepatic encephalopathy
IBS-D: irritable bowel syndrome with diarrhea
SIBO: small intestinal bacterial overgrowth
TD: travelers' diarrhea

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose*
azithromycin (Zithromax®)	**TD** 1,000 mg PO single dose	500 mg/day PO is FDA-approved dosage; however, doses up to 1,200 mg/day PO are used off-label; 2 g PO when given as single dose
lactulose (Enulose®)	**HE** 30 to 45 mL, containing 20 g to 30 g of lactulose), PO TID-QID; may be adjusted every day or two to produce 2 or 3 soft stools daily	Specific maximum dosage information is not available
dicyclomine (Bentyl®)	**IBS-D** 20 mg PO QID	160 mg/day
hyoscyamine (Levsin®, Levbid®)	**IBS-D** Levsin: 0.125 – 0.25 mg PO Q 4h Levbid: 0.375 – 0.75 mg PO Q 12 h	1.5 mg/day
loperamide (Imodium A-D®)	**IBS-D** 2 to 4 mg PO up to QID	16 mg/day
diphenoxylate/ atropine (Lomotil®)	**IBS-D** Initially, 5 mg (2 tablets) PO QID; Discontinue after 10 days if clinical improvement is not observed	20 mg/day (of diphenoxylate)

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Maximum dose of the drug, not indication specific*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of Xifaxan
- Boxed warning(s): none reported

Appendix D: General Information

- Per the 2014 hepatic encephalopathy practice guidelines by the American Association for the Study of Liver Diseases, rifaximin is recommended as an add-on to lactulose to prevent overt HE recurrence. No solid data support the use of rifaximin alone. In the clinical trials for approval of Xifaxan for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed.

- Xifaxan 550 mg TID dosing regimens may be appropriate in the treatment of SIBO for patients with documented IBS. A trial by Scarpellini, et al. (2007) compared 80 adult patients with SIBO randomized to either 1,200 mg/day or 1,600 mg/day of Xifaxan for 7 days. 78.75% of the patient group had IBS. Using glucose breath test (GBT) normalization as an indicator for improved SIBO, 80% of patients on 1,600 mg/day had normalized GBT, compared to 58% of patients on 1,200 mg/day ($p < 0.05$, OR 1.82, 95% CI 1.09–8.01).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HE	550 mg PO BID	1,100 mg daily
IBS-D	550 mg PO TID for 14 days	1,650 mg daily
TD	Adults and children ≥ 12 years of age: 200 mg PO TID for 3 days	600 mg daily
SIBO	200 mg PO TID for 7 days Or 550 mg PO BID for 14 days 550 mg PO TID for 7 days may be considered in patients with SIBO and IBS	1,650 mg daily

VI. Product Availability

Tablets: 200 mg, 550 mg

VII. References

1. Xifaxan Prescribing Information. Bridgewater, NJ: Salix Pharmaceuticals; October 2020. Available at https://www.xifaxan.com/. Accessed July 26, 2022.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: https://www.clinicalkey.com/pharmacology.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed July 26, 2022.

Hepatic Encephalopathy

4. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by AASLD-EASL. Hepatology. 2014; 60 (2): 715-735. Available at: https://www.aasld.org/sites/default/files/2019-06/hepaticencephalopathy82014.pdf.

Irritable Bowel Syndrome

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Travelers' Diarrhea

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10. Centers for Disease Control and Prevention. CDC 24/7: Saving Lives. Protecting People. Chapter 2 Travelers' Diarrhea. Last reviewed November 22, 2019. Accessed July 26, 2022. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2020/preparing-international-travelers/travelers-diarrhea.

Small Intestinal Bacterial Overgrowth

11. Pimentel M, Saad RJ, Long MD, et al. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. Am J Gastroenterol 2020;115:165-178. Available at: https://doi.org/10.14309/ajg.0000000000000501.

12. Lauritano EC, Gabrielli M, Lupascu A, et al. Xifaxan Dose-Find Study for the Treatment of Small Intestinal Bacterial Overgrowth. Aliment Pharmacol Ther. 2005 Jul 1;22(1):31-35.
13. Cuoco L, Salvagnini M. Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin. Min Gastroentero Dietol. 2006;52(1):89-95.
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Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2018 annual review: no significant changes; references reviewed and updated.	07.20.18	11.18
Requirement for a prior trial of a fluoroquinolone is removed due to concerns regarding increasing resistance to fluoroquinolones along with adverse dysbiotic (reduction in diversity of intestinal microbiota) and musculoskeletal adverse effects.	04.23.19	05.19
4Q 2019 annual review: no significant changes; for SIBO added requirement for age 12 or older; clarified for IBS-D continuation requests no more than 3 treatment courses started within the last 6 months; references reviewed and updated.	08.08.19	11.19
4Q 2020 annual review: deleted off-label Crohn's disease criteria set as use is not supported by treatment guidelines https://acgcdn.gi.org/wp-content/uploads/2018/04/ACG-Crohns-Guideline-Summary.pdf; references reviewed and updated.	07.22.20	11.20
4Q 2021 annual review: no significant changes; references reviewed and updated.	08.12.21	11.21
4Q 2022 annual review: added requirement for concurrent lactulose and rifaximin to initial criteria for HE per guidelines; references reviewed and updated.	07.26.22	11.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.