Clinical Policy Title:	rifaximin
Policy Number:	RxA.314
Drug(s) Applied:	Xifaxan®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Rifaximin (Xifaxan®) is a rifamycin antibacterial. It 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.*

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
rifaximin (Xifaxan®)	HE	550 mg by mouth twice daily	1,100 mg daily
	IBS-D	550 mg by mouth three times daily for 14 days. Patients who experience recurrence can be retreated up to 2 times with the same regimen.	1,650 mg daily
	TD	Adults and children ≥ 12 years of age: 200 mg by mouth three times daily for 3 days	600 mg daily

Dosage Forms

- Tablets: 200 mg, 550 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Hepatic Encephalopathy (must meet all):

1. Diagnosis of HE and prescribed for reducing risk of overt HE recurrence;
2. Age 18 years or older;
3. Member meets a or b:
   a. Xifaxan is prescribed as add-on to lactulose therapy;
   b. 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. Dose does not exceed 1,100 mg per day (2 tablets per day).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Irritable Bowel Syndrome with Diarrhea (must meet all):
1. Diagnosis of IBS-D;
2. Age 18 years or older;
3. Failure of any two of the following, each from a different drug class, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced:
   a. anti-diarrheal agent (e.g., loperamide);
   b. antispasmodic (e.g., dicyclomine, hyoscyamine);
   c. Tricyclic antidepressant (e.g., amitriptyline, nortriptyline, imipramine, etc.)
4. Dose does not exceed 1,650 mg per day (3 tablets per day).

Approval Duration
Commercial: 14 days
Medicaid: 14 days

C. Travelers' Diarrhea (must meet all):
1. Diagnosis of TD;
2. Age 12 years or older;
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 per day (3 tablets per day).

Approval Duration
Commercial: 3 days
Medicaid: 3 days

D. Small Intestinal Bacterial Overgrowth (off-label) (must meet all):
1. Diagnosis of small intestinal bacterial overgrowth (SIBO);
2. Age 12 years or older;
3. Failure of systemic antibiotic such as ciprofloxacin, norfloxacin, tetracycline, and trimethoprim-sulfamethoxazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 1,650 mg per day (3 tablets per day).

Approval Duration
Commercial: 14 days
Medicaid: 14 days

E. Crohn's Disease (off-label) (must meet all):
1. Diagnosis of Crohn's disease;
2. Age 18 years or older;

3. Failure of metronidazole or ciprofloxacin, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 1,600 mg per day.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

II. Continued Therapy Approval

A. Hepatic Encephalopathy (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Xifaxan® is being used 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 per day (2 tablets per day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Irritable Bowel Syndrome with Diarrhea (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member has not had greater than 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 per day (3 tablets per day).

Approval Duration
Commercial: 14 days
Medicaid: 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
Commercial: Not Applicable
Medicaid: Not Applicable

D. Small Intestinal Bacterial Overgrowth (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 1,650 mg per day (3 tablets per day).

Approval Duration
Commercial: Up to 14 days
Medicaid: Up to 14 days

E. Crohn's Disease (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;

2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 1,600 mg per day.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

III. Appendices

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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
ciprofloxacin (Cipro®)	**Crohn's disease** 500 mg by mouth twice daily	1.5 g/day (regular release)
azithromycin (Zithromax®)	**TD** 1,000 mg by mouth single dose	500 mg/day by mouth is FDA-approved dosage; however, doses up to 1,200 mg/day by mouth are used off-label; 2 g by mouth when given as single dose
lactulose (Enulose®)	**HE** 30 to 45 mL, containing 20 g to 30 g of lactulose), by mouth three times a day - four times a day; 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 by mouth four times a day	160 mg/day
loperamide	**IBS-D** 2 to 4 mg by mouth up to four times a day	16 mg/day
metronidazole (Flagyl®)	**Crohn's disease** 200 to 600 mg three times a day for 3 to 6 months	4 g/day

*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

- 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.
- 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.
- Xifaxan® 550mg 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 1200mg/day or 1600mg/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 1600mg/day had normalized GBT, compared to 58% of patients on 1200mg/day ($P < 0.05$, OR 1.82, 95% CI 1.09–8.01).

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Updated initial approval criteria I.A.2 for hepatic encephalopathy in specify lactulose monotherapy. 3. Updated initial approval criteria I.D.3 for SIBO to include failure of systemic antibiotic. 4. Continued therapy criteria II.A.1, B.1, C.1, D.1, E1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 5. Approval duration was updated to include commercial, Medicaid and HIM plan in initial approval as well as in clinical therapy criteria. 6. References were updated.	08/26/2020	09/14/2020
Policy was reviewed: 1. Dosing Information for off label indications removed. 2. Continued therapy criteria II.A.1, B.1, C.1, D.1, E.1 was rephrased to "Member is curretly...". 3. HIM deleted as per update. 4. APPENDIX B: Therapeutic Alternatives verbiage changed to "Below are suggested..". 5. Updated initial approval criteria under I.A.3, and I.B.3 6. References were reviewed and updated.	04/12/2021	06/10/2021