Clinical Policy: Rifaximin (Xifaxan)

Reference Number: CP.PMN.47
Effective Date: 11.01.11
Last Review Date: 11.18
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Rifaximin (Xifaxan®) is a rifamycin antibacterial.

FDA Approved Indication(s)

Xifaxan is indicated for:

- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults
- Treatment of travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older

Limitation(s) of use in 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 *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.

It is the policy of health plans affiliated with Centene Corporation® 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 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:
HIM/Medicaid – 6 months
Commercial – Length of Benefit

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 (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 per day (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 one of the following fluoroquinolone regimens, unless contraindicated or clinically significant adverse effects are experienced (a, b, or c):
   a. Ciprofloxacin 500 mg twice daily for 1-3 days;
   b. Levofloxacin 500 mg once daily for 1-3 days;
   c. Ofloxacin 200 mg twice daily for 1-3 days;
4. Failure of azithromycin 1,000 mg as a single dose, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 600 mg per day (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. Dose does not exceed 1650 mg per day (3 tablets per day).

Approval duration: Up to 14 days

E. Crohn`s Disease (off-label) (must meet all)**:**

1. Diagnosis of Crohn`s Disease;
2. Age ≥ 18 years;
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: 12 weeks

F. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Hepatic Encephalopathy (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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:
HIM/Medicaid – 12 months
Commercial – Length of Benefit

B. Irritable Bowel Syndrome with Diarrhea (IBS-D) (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member has not had ≥ three 14-day treatment courses in the last 6 months;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 1650 mg per day (3 tablets per day).

Approval duration: 14 days

C. Travelers' Diarrhea (must meet all)**:**
1. May not be renewed as maximum allowed treatment duration is 3 days. 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 Centene benefit 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 per day (3 tablets per day).

Approval duration: Up to 14 days

E. Crohn`s Disease (off-label) (must meet all)**:**
1. Currently receiving medication via a Centene benefit 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 1,600 mg per day.

Approval duration: 12 weeks

F. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies –

CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose*
ciprofloxacin (Cipro®)	**TD** 500 mg PO BID for 1 to 3 days **Crohn's disease** 500 mg PO BID	1.5 g/day (regular release)
levofloxacin (Levaquin®)	**TD** 500 mg PO QD for 1 to 3 days	Usually 750 mg/day; occasionally higher dosages have been suggested
ofloxacin	**TD** 200 mg PO BID for 1-3 days or 400 mg PO as a single dose or once daily for 3 days	800 mg/day
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
loperamide	**IBS-D** 2 to 4 mg PO up to QID	16 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose*
metronidazole (Flagyl®)	**Crohn's disease** 200 to 600 mg TID 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 C: 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).

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
Crohn's disease	200 mg PO TID or 800 mg PO BID	1,600 mg daily

VI. Product Availability

Tablets: 200 mg and 550 mg

VII. References

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14. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 16, 2018.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Updated reference. Concurrent use of lactulose language clarified.	12.14	12.14
Updated references.	04.15	04.15
Converted to new guideline Updated indications to match prescribing information (including ages of approval). Removed requirement for identification of causative pathogen within traveler's diarrhea (included use for E. coli as informational only as culture availability is limited). Reworded requirements for clarity. Clarified requirement for lactulose for	08.15	08.15

Reviews, Revisions, and Approvals	Date	P&T Approval Date
hepatic encephalopathy. Added criteria for IBS-D, renewal information, and supporting references.		
Updated template and references. Added requirement for previous fulfilment of Centene coverage criteria for continued approval. Added option for failure of levofloxacin for travelers' diarrhea. Clarified continuation requirement for travelers' diarrhea. Modified specific max dosing criteria to generalized statement. Added workflow document.	05.16	08.16
Converted to new template. Modified generalized FDA maximum recommended dosing statement to specific max dosing criteria; Updated references to reflect current practice guidelines. -Hepatic encephalopathy: Modified continued criteria to require concurrent use of Xifaxan and lactulose (vs requiring use of lactulose in the last 90 days) per AASLD guidelines. -Travelers' diarrhea: Corrected fluoroquinolone trial/failure option to ciprofloxacin 500 mg twice daily x 1-3 days or levofloxacin 500 mg once daily x 1-3 days (vs ciprofloxacin or levofloxacin 500 mg twice daily x 1-3 days). Added additional fluoroquinolone trial/failure option of ofloxacin 200 mg twice daily x 1-3 days per IDSA guidelines. Removed trial/failure option of azithromycin 500 mg x 3 days as the single 1000 mg dose is recommended per IDSA guidelines. Modified trial/failure criteria to require one fluoroquinolone AND azithromycin.	09.16	11.16
References reviewed and updated	11.27.17	11.17
3Q 2018 annual review: policies combined for Commercial, HIM, and Medicaid lines of business; no significant changes from previously approved corporate policy; commercial: added age requirement; for IBS-D, removed trial/failure option of bulk forming agent; for TD: added additional fluoroquinolone trial/failure options per guideline, and azithromycin trial; HIM: added age requirement; for TD, added additional fluoroquinolone trial/failure option of ofloxacin 200 mg twice daily x 1-3 days per IDSA guidelines; Medicaid: for IBS-D, modified trial/failure requirement of either loperamide or bile acid sequestrant to loperamide and antispasmodic agent, removed timeframe in which trial must have occurred; HIM/Medicaid: for IBS-D, modified number of total treatment courses from 2 to 3 on re-auth per PI; added off-label criteria for SIBO and Crohn's disease; references reviewed and updated.	04.18.18	08.18
4Q 2018 annual review: no significant changes; references reviewed and updated.	07.20.18	11.18

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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