Clinical Policy: Rifaximin (Xifaxan)

Reference Number: CP.CPA.171
Effective Date: 11.16.16
Last Review Date: 11.17 Revision Log
Line of Business: Medicaid – Medi-Cal

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

Description
Rifaximin (Xifaxan®) is an oral rifamycin antibiotic structurally related to rifampin.

FDA approved indication
Xifaxan tablet is indicated:

- For the treatment of patients ≥ 12 years of age with travelers' diarrhea caused by noninvasive strains of *Escherichia coli.*
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults

Limitation of use: Xifaxan tablets 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 (which may include office chart notes and lab results) 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. Travelers` Diarrhea (must meet all)**:**

1. Diagnosis of Travelers' Diarrhea;
2. One of the following (a or b):
   a. Patient is 18 years or older with failure to ciprofloxacin unless contraindicated or clinically significant adverse effects are experienced;
   b. Patient is 12-17 years of age;
3. Dose does not exceed 600 mg/day PO.

Approval duration: 7 days

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

1. Prescribed for the treatment or prophylaxis of hepatic encephalopathy;
2. Failure of lactulose unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 1100 mg/day PO.

Approval duration: Length of Benefit

C. Small Intestinal Bacterial Overgrowth (must meet all)**:**
1. Diagnosis of Small Intestinal Bacterial Overgrowth;
2. Dose does not exceed 1650 mg/day PO.

Approval duration: Up to 14 days

D. Crohn`s Disease (must meet all)**:**
1. Diagnosis of Crohn`s Disease;
2. Failure to metronidazole or ciprofloxacin unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 1600 mg/day PO.

Approval duration: 12 weeks

E. IBS-D (Irritable Bowel Syndrome with Diarrhea) (must meet all)**:**
1. Diagnosis of IBS-D (Irritable Bowel Syndrome with Diarrhea);
2. Failure to therapy from two different classes from the following list, unless contraindicated or clinically significant adverse effects are experienced:
   a. Bulk forming agent (e.g., psyllium);
   b. Anti-diarrhea agent (e.g., bismuth subsalicylate, loperamide);
   c. Antispasmodic agent (e.g., diphenoxylate-atropine, dicyclomine, hyoscyamine, hyoscyamine/atropine/scopolamine/phenobarbital);
3. Dose does not exceed 1650 mg/day PO.

Approval duration: 14 Days

F. Other diagnoses/indications
1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

II. Continued Therapy

A. All indications in Section I (must meet all)**:**
1. Currently receiving medication via a Centene benefit or member has previously met initial approval criteria
2. Dose does not exceed:
   a. Travelers diarrhea: 600 mg/day PO
   b. Hepatic Encephalopathy: 1100 mg/day PO
   c. IBS-D: 1650 mg/day
   d. Small Intestinal Bacterial Overgrowth: 1650 mg/day PO
   e. Crohn's Disease: 1600 mg/day PO

Approval duration:

Travelers' diarrhea: 7 days
Hepatic Encephalopathy: Length of benefit
Small Intestinal Bacterial Overgrowth: Up to 14 days
Crohn's Disease: 14 days
IBS-D: 14 days (Patients who experience recurrence can be retreated up to two times with the same regimen)

B. 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 CP. PMN.53 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 – CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

HE: overt hepatic encephalopathy
IBS-C: irritable bowel syndrome with constipation
IBS-D: irritable bowel syndrome with diarrhea
SIBO: small intestinal bacterial overgrowth
GBT: glucose breath test

Appendix B: General Information

- 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*.
- Xifaxan should be discontinued if diarrhea persists or worsens following 24-48 hours of therapy. An alternative antibiotic should be considered.
- Xifaxan is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration.
- Further investigation is warranted to determine efficacy in diverticulitis and inflammatory bowel disease.
- There is not enough evidence available to support the use of Xifaxan for C. Difficile infections. C. Diff is not recognized as a valid off-label indication for Xifaxan in either Micromedex or Clinical Pharmacology. One study of 20 patients and one case series of 8 patients are available looking at Xifaxan for this indication, but there is not enough data presented to support approval.
- Xifaxan should not be used as a second course of therapy for the same incident of travelers` diarrhea secondary to concerns of resistance.
- The FDA approval for IBS-D was based on data from three clinical studies of more than 3,000 patients. Results of TARGET 1 and 2 showed patients treated with Xifaxan 550 mg achieved relief of the FDA composite endpoint (stool consistency and abdominal pain) versus placebo. TARGET 3 showed that patients who responded to treatment with Xifaxan 550 mg but experienced recurrent symptoms responded to repeat treatment in the FDA composite endpoint versus placebo. Xifaxan is not FDA approved indicated for irritable bowel syndrome with constipation(IBS-C). Xifaxan should not be initiated in patients with constipation.
- 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).

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dose/Limit/ Maximum Dose
ciprofloxacin	**Traveler`s diarrhea**: 500 mg PO BID for up to 3 days	6 tablets
	Infectious diarrhea, ≥ 18 yrs: 500 mg to 750mg PO BID for 3 – 7 days	14 tablets
Various brands (neomycin)	**Hepatic Encephalopathy**: 4 gm-12 gm PO QD	12 gm/day
Various brands (lactulose)	**Hepatic Encephalopathy**: 30-45 ml PO TID-QID	N/A
dicyclomine (Bentyl®)	**IBS-D**: Adults: 80mg/day PO divided QID then increase to 160 mg/day. If efficacy not achieved in 2 weeks, therapy should be discontinued	160 mg/day
hyoscyamine (Levsin®, Levbid®, Hyosyne, Anaspaz)	**IBS-D:** Adults: Levsin: 0.125 – 0.25 mg PO Q 4h Levbid: 0.375 – 0.75 mg PO Q 12h	1.5 mg/day
hyoscyamine, atropine, scopolamine, phenobarbital (Donnatal®, Phenogytro	**IBS-D:** Adults: Donnatal: 1-2 tablets or 5-10 ml of elixir PO TID-QID Donnatal Extentabs: 1 tablet PO Q 12h; may increase to 1 tablet PO Q 8h if needed	2 tablets or 10 mL per day
Loperamide (Imodium®)	**IBS-D**: Adults: 4 mg PO followed by 2mg after each unformed stool until diarrhea is resolved; then individualize dose. Administer optimal daily dose (4-8 mg) as single or divided doses.	If no clinical improvement after treatment with 16 mg/day for at least 10 days, symptoms are unlikely to be controlled by further use.
Diphenoxylate/ atropine (Lomotil®)	**IBS-D:** Initial dose 5 mg PO QID. Individualize dose.	If no clinical improvement after treatment with 20 mg/day for at least

		10 days, symptoms are unlikely to be controlled by further use.

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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Traveler's Diarrhea	Adults and children ≥ 12 years of age: 200 mg PO TID for 3 days	600 mg/day PO
Hepatic Encephalopathy	550 mg PO BID	1100 mg/day PO
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	1650 mg/day PO
SIBO with IBS	550 mg PO TID for 7 days	1650 mg/day PO
Crohn's disease	200 mg PO TID or 800 mg PO BID	1600 mg/day PO
IBS-D	550 mg PO TID	1650 mg/day PO

VI. Product Availability

Tablet: 200 mg, 550 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Minor changes to verbiage and grammar. References updated.	05.24.17	11.17
Update approval duration for SIBO to state "Up to" 14 days	10.18.17	

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.

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