BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 8/02/18**
	LAST CRITERIA REVISION DATE: 8/02/18
	ARCHIVE DATE:

XIFAXAN® (rifaximin) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

XIFAXAN® (rifaximin) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Xifaxan (rifaximin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 12 years of age or older
  2. A confirmed diagnosis of **Travelers' diarrhea** caused by noninvasive strains of *Escherichia coli*
  3. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **EITHER** azithromycin **OR** ciprofloxacin **OR** levofloxacin
  4. There are **NO** contraindications:
     - Contraindications include:
       - History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of Xifaxan
  5. Will not be used for diarrhea complicated by fever or blood in stool
  6. Will not be used for diarrhea caused by bacteria other than *Escherichia coli*
  7. Will not be used for diarrhea associated with use of antibiotics

  Initial approval duration:
  200 mg three times a day for 3 days, one time approval per Travelers' diarrhea, no refills
  No other dose, frequency, or duration will be approved

- **Criteria for initial therapy:** Xifaxan (rifaximin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 18 years of age or older
  2. A confirmed diagnosis of **overt hepatic encephalopathy**
  3. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **EITHER** lactulose **OR** neomycin **OR** metronidazole
  4. There are **NO** contraindications
     - Contraindications include:
       - History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of Xifaxan
  5. Will not be used for diarrhea complicated by fever or blood in stool
  6. Will not be used for diarrhea caused by bacteria other than *Escherichia coli*

XIFAXAN® (rifaximin) oral tablet (cont.)

7. Will not be used for diarrhea associated with use of antibiotics

Initial approval duration:
550 mg two times a day
No other dose or frequency will be approved

- **Criteria for initial therapy:** Xifaxan (rifaximin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual is 18 years of age or older
2. A confirmed diagnosis of moderate to severe **Irritable Bowel Syndrome with Diarrhea** with symptoms of moderate abdominal pain, discomfort and bloating
3. The recurrent symptoms are present, on average, at least 1 day per week during the preceding month associated with 2 or more of the following: related to defecation, associated with a change in stool frequency, associated with a change in stool form/appearance
4. The abnormal diarrheal bowel movements are Bristol Stool Form Scale (BSFS) type 6 or 7
5. Failed dietary modification that includes lactose restricted diet, if lactose-intolerant; exclusion of gas-producing foods; low carbohydrate diet and elimination of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs)
6. Individual has failure, contraindication or intolerance to **BOTH** dicyclomine **and** hyoscyamine
7. Individual has failure, contraindication or intolerance to **EITHER** amitriptyline **OR** nortriptyline
8. Will not be used for diarrhea complicated by fever or blood in stool
9. Will not be used for diarrhea caused by bacteria other than *Escherichia coli*
10. Will not be used for diarrhea associated with use of antibiotics
11. There are **NO** contraindications:
    - Contraindications include:
      - History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of Xifaxan

Initial approval duration:
550 mg three times a day for 14 day course with two refills
No other dose, frequency, or duration will be approved

XIFAXAN® (rifaximin) oral tablet (cont.)

- **Continuation of coverage (renewal request):** Xifaxan (rifaximin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual's condition responded while on therapy
   - **Response for overt hepatic encephalopathy** is defined as **TWO** of the following:
     - Achieved and maintains no asterixis tremors or only few asterixis flaps
     - Achieved and maintains at least a 50% reduction in neurologic dysfunction, seen as a reduction in lethargy or apathy, disorientation for time or place, inappropriate behavior, euphoria or anxiety, somnolence, or coma
     - Achieved and maintains at least a 50% reduction in overt hepatic encephalopathy hospitalizations

2. Individual has been adherent with the medication

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

Renewal duration:

For Overt Hepatic Encephalopathy:

550 mg two times a day for 1 year
No other dose or frequency will be approved

Description:

Xifaxan (rifaximin) is indicated for the treatment of: i) Travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli (E. coli)* in adults and pediatric patients 12 years of age and older; ii) reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults; and iii) irritable bowel syndrome with diarrhea (IBS-D) in adults. It should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

Xifaxan (rifaximin) is a semi-synthetic, non-aminoglycoside, non-systemic antibiotic and is structural analog of rifampin. Rifaximin acts by binding to the beta-subunit of the bacterial DNA-dependent RNA polymerase blocking one of the steps in transcription to inhibit bacterial RNA synthesis. The result is inhibition of bacterial protein synthesis and consequently it inhibits the growth of bacteria. It has been shown to be active against *E. coli.*

According to the Centers for Disease Control (CDC), bacteria are the most common cause of TD. TD is rarely life threatening, but it can be severely debilitating in children and the elderly, as severe dehydration can occur. The most common pathogen is enterotoxigenic *E. coli*, followed by *Campylobacter jejuni*, *Shigella* species and *Salmonella* species. Antibiotics are used in the treatment of TD and are effective in cases caused by bacterial pathogens as long as they are susceptible to the particular antibiotic prescribed. Microbial resistance to antibiotics is on the rise and is dependent on many factors one of which is area traveled. First-line antibiotics are those in the fluoroquinolone class of agents, which includes ciprofloxacin or levofloxacin. Potential alternative to the fluoroquinolones class includes azithromycin and rifaximin with selection based on suspected pathogen.

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HE is a syndrome characterized by personality changes, intellectual impairment, and a depressed level of consciousness. In HE there is the occurrence of confusion, altered level of consciousness, and coma as a result of liver failure. The 2014 American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) practice guideline define HE as a brain dysfunction caused by liver insufficiency and manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma. The guideline states that lactulose has been shown to reduce recurrence of HE after an episode of overt HE and it can prevent the development of the first episode. It is considered the agent of first choice for episodic overt HE. Rifaximin is considered add-on therapy to lactulose for prevention of overt HE. AASLD & EASL state that neomycin and metronidazole are alternatives choices for the treatment of over HE.

Irritable bowel syndrome (IBS) or spastic colon is a symptom-based diagnosis. It is characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. Diarrhea or constipation may predominate and are designated as IBS-D or IBS-C, respectively. Treatment is determined by the predominant symptom. Milder, less frequent episodes may be managed with dietary modifications such as eliminating or minimizing foods that worsen symptoms (such as those that contain caffeine, lactose, or artificial sweeteners for IBS-D).

A 2014 guideline from the American Gastroenterology Association (AGA) makes several recommendations on the treatment of IBS-D. The AGA guideline suggests using rifaximin, loperamide, tricyclic antidepressants, and antispasmodic agents. Lifestyle measures are also recommended for IBS and include stress management and dietary interventions such as a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAP). FODMAPs are incompletely absorbed in the small intestine and ferment in the colon. They include foods with fructose (such as apples, pears, honey, high-fructose corn syrup), lactose (milk), fructans or galactans (wheat, onions), and polyols (some fruits and vegetables, artificial sweeteners such as sorbitol). Individuals with IBS may see symptom improvement with gluten restriction. This may be due to the fact that gluten is found in wheat, a high FODMAP food. Recent data confirms a role for probiotics in IBS, but also makes it clear that the effects of probiotics in IBS are highly strain-specific.

Guidelines recommend non-pharmacologic and over-the-counter therapy as first line therapy for IBS-D. Antispasmodics such as dicyclomine and hyoscyamine reduce abdominal spasms and cramps through reduced smooth muscle contractions. They may improve pain and global symptoms. Their efficacy is based on continuous use and the effect is rated as modest. Tricyclic antidepressants (amitriptyline, nortriptyline) improve abdominal pain and GI symptoms. Modest improvements may not be seen for several weeks. Loperamide may improve abdominal pain, stool consistency & frequency, but may require continuous use.

Definitions:

Irritable Bowel Syndrome (Rome IV criteria)

Recurrent abdominal pain, on average, at least one day per week during the preceding month with two or more of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Bristol Stool Form Scale (BSFS)

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Seven types of stool are:

- Type 1: Separate hard lumps, like nuts (hard to pass); also known as *goat feces*
- Type 2: Sausage-shaped, but lumpy
- Type 3: Like a sausage but with cracks on its surface
- Type 4: Like a sausage or snake, smooth and soft
- Type 5: Soft blobs with clear cut edges (passed easily)
- Type 6: Fluffy pieces with ragged edges, a mushy stool
- Type 7: Watery, no solid pieces, entirely liquid

Types 1 & 2 indicate constipation
Types 3 & 4 indicate the ideal stools (especially the latter)
Types 5, 6 & 7 specify diarrheal stools

Irritable bowel syndrome (IBS) with predominant diarrhea (IBS-D)
Abnormal bowel movements are usually diarrhea (BSFS type 6 and 7)
More than 25% of BM with BSFS types 6 or 7 and less than 25% of BM with BSFS types 1 or 2
Based on the patient's reported predominant bowel habit on days with abnormal bowel movements
Off laxatives and off antidiarrheal agents

IBS with predominant constipation (IBS-C)
More than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2
Less than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7
Based on the patient's reported predominant bowel habit on days with abnormal bowel movements
Off laxatives and off antidiarrheal agents

IBS with mixed bowel habits (IBS-M)
More than one fourth (25%) of bowel movements with Bristol stool form types 1 or 2 and
More than one-fourth (25%) of bowel movements with Bristol stool form types 6 or 7
Based on the patient's reported predominant bowel habit on days with abnormal bowel movements
Off laxatives and off antidiarrheal agents

IBS unclassified (IBS-U)
Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified
Based on the patient's reported predominant bowel habit on days with abnormal bowel movements
Off laxatives and off antidiarrheal agents

Resources:

Vilstrup H, Amodio P, Bajaj J, et al.: Practice Guideline: Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by AASLD and EASL

Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S: American Gastroenterology Association Institute Guideline on the Pharmacological Management of Irritable Bowel Syndrome. Gastroenterol 2014; 147:1146-1148

XIFAXAN® (rifaximin) oral tablet (cont.)

Xifaxan. Package Insert. Revised by manufacturer 11/2015. Accessed and reviewed on 05-23-2016, 07-10-2017

Xifaxan. Package Insert. Revised by manufacturer 05/2015. Accessed and reviewed on 06-23-2015

Xifaxan. Package Insert. Revised by manufacturer 03/2014. Accessed 05-08-2015

Xifaxan. Package Insert. Revised by manufacturer 01/2018. Accessed 07-02-2018

World Gastroenterology Organization Global Guidelines: Irritable Bowel Syndrome: A global Perspective Update September 2015

Weinberg DS, Smalley W, Heidelbaugh JJ, and Sultan S.: American Gastroenterological Association Institute Guideline on the Pharmacological Management of Irritable Bowel Syndrome. Gastroenterology 2014; 147:1146-1148

Ford AC, Moayyedi P, Lacy BE, et al.: American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. Am J Gastroenterol 2014; 109 Aug Suppl 1:S2-S26

Lacy BE, Mearin F, Chang L, et al.: Bowel Disorders. Gastroenterology 2016; 150 (6):1393-1407

UpToDate: Travelers' diarrhea: Clinical manifestations, diagnosis, and treatment. Current through May, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/travelers-diarrhea-clinical-manifestations-diagnosis-and-treatment?search=travelers%20diarrhea&source=search_result&selectedTitle=1~105&usage_type=default&display_rank=1#H1037168843

UpToDate: Travelers' diarrhea: Microbiology, epidemiology, and prevention. Current through May, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/travelers-diarrhea-microbiology-epidemiology-and-prevention?search=travelers%20diarrhea&source=search_result&selectedTitle=2~105&usage_type=default&display_rank=2

UpToDate: Hepatic encephalopathy in adults: Clinical manifestations and diagnosis. Current through May, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/hepatic-encephalopathy-in-adults-clinical-manifestations-and-diagnosis?search=hepatic%20encephalopathy&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Hepatic encephalopathy in adults: Treatment. Current through May, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/hepatic-encephalopathy-in-adults-treatment?search=hepatic%20encephalopathy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Treatment of irritable bowel syndrome in adults. Current through Mar, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-irritable-bowel-syndrome-in-adults?search=irritable%20bowel%20syndrome%20with%20diarrhea&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

XIFAXAN® (rifaximin) oral tablet (cont.)

UpToDate: Clinical manifestations and diagnosis of irritable bowel syndrome in adults. Current through Mar, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-manifestations-and-diagnosis-of-irritable-bowel-syndrome-in-adults?search=irritable%20bowel%20syndrome&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H2263560866

UpToDate: Pathophysiology of irritable bowel syndrome. Current through Mar, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/pathophysiology-of-irritable-bowel-syndrome?search=irritable%20bowel%20syndrome&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

UpToDate: Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis. Current through Mar, 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/small-intestinal-bacterial-overgrowth-clinical-manifestations-and-diagnosis?sectionName=Jejunal%20aspirate%20culture&topicRef=2629&anchor=H894085110&source=see_link#H894085110

FDA-approved indication and dosage:

<table>
<tr><th>Indication</th><th>Recommended Dose</th></tr>
<tr>
<td>XIFAXAN is a rifamycin antibacterial indicated for:
• 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

<u>Limitations of Use</u>
• 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</td>
<td>
<table>
<tr><th>Condition</th><th>Recommended Dosage Regimen</th></tr>
<tr><td>TD</td><td>One 200 mg tablet 3 times a day for 3 days</td></tr>
<tr><td>HE</td><td>One 550 mg tablet 2 times a day</td></tr>
<tr><td>IBS-D</td><td>One 550 mg tablet 3 times a day for 14 days. Patients who experience recurrence can be retreated up to two times with the same regimen.</td></tr>
</table>
• XIFAXAN can be taken with or without food.
</td>
</tr>
</table>

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.