BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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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.**

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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. Failure, intolerance, or contraindication to **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. Failure, intolerance, or contraindication to **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*

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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 3 months 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. Failure, intolerance, or contraindication to **BOTH** dicyclomine **and** hyoscyamine
7. Failure, intolerance, or contraindication 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

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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.

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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:

Traveler's Diarrhea:

J Travel Med 2017: Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report		
Azithromycin	1000 mg once OR 500 mg once daily for 3 days	Preferred for dysentery (diarrhea with the presence of blood and mucus) or febrile diarrhea & pregnant women
Levofloxacin	500 mg once OR 500 mg once daily for 3 days	Fluoroquinolones are associated with multiple adverse effects

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Ciprofloxacin	750 mg once OR 500 mg twice daily for 3 days	
Ofloxacin	400 mg once OR 400 mg once daily for 3 days	
Rifaximin	200 mg three times daily for 3 days	Not for use with dysentery or febrile diarrhea
Rifamycin	388 mg twice daily for 3 days	

Hepatic encephalopathy:
Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma. Overt hepatic encephalopathy is diagnosed clinically based on two types of symptoms: impaired mental status, as defined by the West Haven Criteria (WHC), and impaired neuromotor function.

West Haven Criteria (also known as Conn Score)		
Minimal (Grade 0)	• No asterixis • No detectable change in behavior • No detectable change in mental status • Minimal encephalopathy	Minimal encephalopathy may not be obvious on clinical examination but can be detected by abnormal results of established psychometric or neuropsychological tests
Grade 1	• Trivial lack of awareness or attention • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers
Grade 2	• Lethargy or apathy • Disorientation for time • Subtle obvious personality change • Amnesia of recent events • Inappropriate behavior • Dyspraxia • Slurred speech • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) $\pm$ the other mentioned symptoms
Grade 3	• Somnolence to semi-stupor • Responsive to verbal stimuli • Confused • Gross disorientation • Bizarre behavior • Clonus • Nystagmus • Positive Babinski sign	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) $\pm$ the other mentioned symptoms
Grade 4	Coma	Does not respond even to painful stimuli

Asterixis grade:
0 = no tremor
1 = few flaps
2 = occasional flaps
3 = frequent flats
4 = continuous flaps

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Irritable Bowel Syndrome (Rome IV criteria)

Recurrent bothersome symptoms of abdominal pain AND altered bowel habit for at least 3 months with symptom onset at least six months before the diagnosis

Recurrent abdominal pain, on average, at least one day per week during the preceding 3 months 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) – assessment performed when not taking laxatives or anti-diarrheal agents only on days with abnormal bowel habits

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

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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:

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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

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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

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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 Jun 2019. 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

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

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