DRUG DETERMINATION POLICY

Title: DDP-04 Miscellaneous Gastrointestinal (GI) Agents

Effective Date: 2/22/23

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve Benefits. Coverage depends on the specific Benefit plan. Pharmacy Benefit Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Xifaxan, Viberzi, Lotronex, and Dificid are indicated for a number of diagnoses. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and disease severity.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

I. Irritable Bowel Syndrome with diarrhea (IBS-D): Xifaxan, Lotronex and Viberzi [must meet all listed below]:

   A. Diagnosis and severity: fulfill Rome IV IBS criteria [see Appendix I].

   B. Other therapies: contraindication, inadequate response after four months or significant adverse effects to over-the-counter and prescription agents listed below:

      1. Over-the-counter agents [must meet one of each drug class listed below]:

         a. Fiber or psyllium

         b. Probiotics.

      2. Prescription agents [must meet one of each drug class listed below]:

         a. Antispasmodics: dicyclomine, hyoscyamine.

         b. Anti-diarrheal medications: loperamide.

         c. Antidepressants: tricyclic, selective serotonin reuptake inhibitors (SSRIs).

C. Dosage regimen

1. Xifaxan (rifaximin) treatment course: 550mg three times per day for two weeks (#42 tabs for two weeks).
2. Lotronex (alesetron): 0.5mg twice daily for four weeks if tolerated, but inadequate response, may increase to 1mg twice daily. If response is inadequate after four weeks of 1mg twice daily, then discontinue treatment.
3. Viberzi (eluxadoline): maximum of 100mg two times daily

D. Approval

1. Initial:
    a. Xifaxan: one course (two weeks)
    b. Lotronex: three months
    c. Viberzi: six months
2. Re-approval: reoccurrence or continued symptoms
    a. Xifaxin: one course (maximum number of times approved is a total of three courses)
    b. Viberzi: one year

E. Exclusions.

1. Lotronex: use in male patients

II. Traveler's Diarrhea: Xifaxan

A. Diagnosis and severity [must meet all listed below]:

1. Symptoms: mild cramps/urgent loose stools to severe abdominal pain, fever, vomiting and bloody diarrhea.
2. Onset: six hours to two days incubation for bacterial and viral pathogens.
3. Travel in high-risk areas: Asia, Middle East, Africa, Mexico and Central/South America.
4. Confirmed diagnosis of *E. coli* (non-invasive).

B. Other therapies: contraindicated, inadequate therapy after two days, or significant adverse effects to one of each drug class listed below:

1. Anti-motility agents: loperamide, diphenoxylate.
2. Antibiotics: azithromycin 1,000mg once or 500mg daily for one to three days.

C. Dosage regimen.

1. Xifaxan (rifaximin oral) treatment course: 200mg three times daily for three days.

D. Approval: one course per initial and repeat episodes.

III. Hepatic Encephalopathy: Xifaxan.

A. Diagnosis and severity [refer to Appendix II]:

1. Severity: Overt hepatic encephalopathy grade II to IV.

B. Treatment indications for Overt hepatic encephalopathy [must meet one listed below]:

1. Active treatment: spontaneous or precipitated episode of hepatic encephalopathy

2. Secondary prophylaxis: post overt hepatic encephalopathy episode

3. Primary prophylaxis: prevent those at high risk for an episode of overt hepatic encephalopathy with cirrhosis.

C. Other therapies: contraindication, inadequate response after four months or significant adverse effects to one below:

1. Lactulose: dose titrated up to three stools per day

D. Dosage regimen for approval:

1. Must be in combination therapy with lactulose unless contraindicated (no Xifaxan mono-therapy)

2. Dose: Xifaxan 550 mg two times daily

E. Approval duration

1. Initial: six months

2. Re-approval: six months

3. Discontinue: precipitating factors controlled, improved liver function or nutritional status

IV. *Clostridioides difficile* Infections: Dificid oral (fidaxomicin)

A. Diagnosis and severity [must meet all listed below]:

1. Diagnosis and severity [must meet both listed below]:

a. Treatment of diarrhea due to *C. difficile*

b. Labs: positive laboratory stool test for *C. difficile* toxin or *C. difficile* toxin B gene

B. Other therapies: contraindication, inadequate response after ten days or significant adverse effects to treatment listed per drug

1. Mild to moderate initial disease: vancomycin (oral)

C. Dosage regimen/approval

1. Initial severe disease and reapproval. Dificid (fidaxomicin): 200mg two times daily for ten days

V. Non-FDA approved indications.

A. Compendium supported (Lexicomp™): compendium support for use of a drug for a non-FDA approved indication.

B. Small Intestinal Bacterial Overgrowth [must meet all criteria listed below]:

1. Age: at least 12 years old

2. Diagnosis and severity [must meet one symptom and aspirate concentration listed below]:

a. Symptoms: bloating, flatulence, abdominal discomfort or chronic watery diarrhea.

b. Jejunal aspirate culture: bacterial concentration of over 10^3 colony forming units/ml.

3. Other therapies: contraindicated, inadequate response after two weeks or significant adverse effects to two different antibiotic classes (e.g., ciprofloxacin, metronidazole, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole).

4. Dosage regimen

a. Xifaxan (rifaximin) treatment course: 550mg three times per day for two weeks (#42 tabs per two weeks).

5. Approval

a. Initial: one course

b. Re-approval: one course (maximum number of times approved is a total of three courses)

4.0 Coding:

None.

5.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Xifaxan, Lotronex Viberzi, Zinplava, Dificid accessed December 2022.
2. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. Am J Gastroenterol 2014;109:S2-S26.
3. American Gastroenterological Association Guideline on the Pharmacological Management of Irritable Bowel Syndrome. Gastroenterol 2014;147:1146-1148.
4. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guidelines by AASLD and EASL.
5. Centers for Disease Control & Prevention (2014).Yellowbook. Chapter 2 - the pre-travel-consultation. Traveler's Diarrhea. Retrieved from http://.cdc.gov/travel/yellowbook/2014.
6. Xifaxan [Package Insert], Whitby, Ontario, Salix; 2015.
7. Guidelines for Diagnosis, Treatment and Prevention of *Clostridium difficile* Infections. Am J of Gastroenterol 2014; 108: 478-498.
8. Bezlotoxumab for Prevention of recurrent *C. difficile* infection. N Engl J Med 2017:376(4); 305-317.
9. UpToDate, Post TW (Ed), Waltham, MA
   - Treatment of Irritable Bowel Syndrome in Adults With Idiopathic Pulmonary Fibrosis. accessed 4/19.

- Treatment of Irritable Bowel syndrome in adults. accessed December 2022.
- Travelers' diarrhea: Clinical manifestations, diagnosis, and treatment LaRocque, R et al. accessed December 2020.
- Clostridioides (formerly Clostridium) difficile infection in adults: Treatment and prevention Kelly, KP et al accessed December 2020.
- Small Intestinal Bacterial Overgrowth: Management. Pimentel et al accessed May 2021.

10. ACG Clinical Guidelines: Prevention, Diagnosis and Treatment of C. difficile Infections Am J of Gastroenterol. 2021;116:1124-1147.
11. Clinical Practice Guidelines by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on the Management of C difficile Infections in Adults. CID 2021:73 (1 September).
12. ACG Clinical Guidelines: Small Intestinal Bacterial Overgrowth. The American Journal of Gastroenterology: February 2020 - Volume 115 - Issue 2 - p 165-178 doi:10.14309/ajg.0000000000000501

6.0 Appendices:

See pages 6-8.

7.0 Revision History:

Original Effective Date: August 26, 2015

Next Review Date: 01/27/2022

Revision Date	Reason for Revision
2/19	Transitioned to new format
12/19	Annual review; replaced abbreviations, reformatting done, revised IBS-D other therapies, updated references as needed.
4/20	Off cycle review; formatting, changed other therapies language, antibiotic treatment for traveler's diarrhea, C. dif lab test, Appendix II, add Dificid to patient safety table.
12/20	Annual review, replaced abbreviations, reformatted, updated references, added Lotronex, approved by P&T 2/24/21
5/21	Off cycle review; clarified instructions, replaced abbreviations, added diagnosis of small intestinal bacterial overgrowth
11/21	Off cycle review, clarified Xifaxan treatment course as two weeks, revised initial severe c. Diff tx to Dificid
02/01/2022	Annual review; Additional changes from Feb P & T; added references
12/22	Annual review; added guidelines; clarified other therapies; removed Zinplava table from coding as it is no longer on formulary

Rome IV Diagnostic Criteria for IBS

- Recurrent abdominal pain, on average, at least 1 day per week in the previous 3 months, associated with 2 or more of the following criteria:
  - Defecation
  - A change in stool frequency
  - A change in stool form (appearance)
- Criteria must be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis

Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

Appendix II: Practice Guideline for Hepatic Encephalopathy in Chronic Liver Disease

TABLE 2. WHC AND CLINICAL DESCRIPTION

WHC INCLUDING MHE	ISHEN	DESCRIPTION	SUGGESTED OPERATIVE CRITERIA	COMMENT
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • 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	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

Appendix III: Monitoring & Patient Safety - Adverse Reactions and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Xifaxan oral rifaximin	• Central Nervous System: headache • Pregnancy Category C	• Central Nervous System: mental status changes (HE) • Genitourinary: blood in stool • Other: temperature, hypersensitivity reaction	None needed
Lotronex oral alosetron	• Gastrointestinal: constipation (9-29%; dose related)	• NA	
Viberzi oral eluxadoline	• Gastrointestinal: constipation (7-8%), nausea (7-8%), abdominal pain (6-7%) • Pregnancy: teratogenicity not seen in animal studies	• Central Nervous System: cognitive/physical impairment in patient with decreased hepatic function • Genitourinary: increased abdominal pain with/without nausea, vomiting, and acute biliary pain with hepatic/pancreatic enzymes	
Dificid fidaxomicin	• Gastrointestinal: nausea (11%) • Miscellaneous: fever (13%)	• NA	