DRUG DETERMINATION POLICY

Title: DDP-04 Miscellaneous Gastrointestinal (GI) Agents

Effective Date: 03/09/2021

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, Dificid and Zinplava are drugs 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 category listed below]:

         a. Fiber or psyllium

         b. Probiotics.

      2. Prescription agents [must meet one of each listed category 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 per 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 discontinue treatment.

3. Viberzi (eluxadoline): maximum of 100mg two times daily.

D. Approval.

1. Initial:

a. Xifaxan: one course.

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 four months, or significant adverse effects to one of each category below:

1. Anti-motility agents: loperamide, diphenoxylate.

2. Antibiotics: azithromycin 1000mg times one dose 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 (HE): Xifaxan.

A. Diagnosis and severity (refer to Appendix II):

1. Severity: Overt HE grade II to IV.

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

1. Active treatment: spontaneous or precipitated episode of HE.

2. Secondary prophylaxis: post Overt HE episode.

3. Primary prophylaxis: prevent those at high risk for an episode of OHE 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 (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 (formerly Clostridium) difficile* Infections (CDI): Dificid oral; Zinplava intravenous.

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

1. Diagnosis [must meet one listed below]:

a. Dificid (fidaxomicin): treatment of diarrhea due to *C. difficile.*

b. Zinplava intravenous (bezlotoxumab IV): adjunct with antibiotic(s) to decrease recurrence in high-risk patients.

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

3. Zinplava: risk of reoccurrence [must meet at least two criteria listed below]:

a. Age: at least 65 years.

b. History of CDI within the previous six months.

c. Immunocompromised.

d. CDI with hyper-virulent strain: ribo-types 027, 078, 244.

e. Severe CDI at presentation: shock, megacolon, perforation, acute renal failure.

B. Other therapies: contraindication, inadequate response after four months or significant adverse effects to treatment listed per drug (see Appendix IV).

1. Dificid (fidaxomicin) [must meet one listed below]:

a. Mild to moderate or recurrent disease: vancomycin (oral).

2. Zinplava intravenous (bezlotoxumab IV) [must meet one listed below]:

a. Severe and complicated disease: vancomycin (oral and rectal) plus metronidazole intravenous.

C. Dosage regimen/approval.

1. Initial:

a. Dificid (fidaxomicin): 200mg two times daily for ten days.

b. Zinplava intravenous (bezlotoxumab IV): 10mg per kg for one dose.

2. Re-approval: Vancomycin for ten days prior to re-approval of Dificid.

4.0 Coding:

AFFECTED CODES				
Code	**brand name**	**Generic name**	**Billing units (1u)**	**Approval**
J0565	Zinplava	bezlotoxumab injections	10mg	Y

5.0 Unique Configuration/Prior Approval/Coverage Details:

None.

6.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Xifaxan, Lotronex Viberzi, Zinplava, Dificid accessed December 2020.
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. Treatment of Irritable Bowel Syndrome in Adults With Idiopathic Pulmonary Fibrosis. UpToDate, Post TW (Ed), Waltham, MA. accessed 4/19.
10. Treatment of Irritable Bowel syndrome in adults. UpToDate Wald, A (Ed), Waltham, MA. accessed December 2020.
11. Travelers' diarrhea: Clinical manifestations, diagnosis, and treatment LaRocque, R et al. UpToDate Waltham, MA. accessed December 2020.
12. Clostridioides (formerly Clostridium) difficile infection in adults: Treatment and prevention Kelly, KP et al UpToDate Waltham, MA. accessed December 2020.

7.0 Appendices:

See pages 6-8.

8.0 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

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: Recommendations for Treatment

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Appendix IV: 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	None Needed
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	None needed
Zinplava IV Bezlotoxumab	• Cardiovascular: exacerbation of heart failure (13%) • Pregnancy: animal reproduction studies not done. monoclonal antibodies pass through the placenta	• None listed	None needed
Dificid fidaxomicin	• Gastrointestinal: nausea (11%) • Miscellaneous: fever (13%)	• None listed	Not needed