# DRUG DETERMINATION POLICY

**Title:** DDP-04 Miscellaneous Gastrointestinal (GI) Agents

**Effective Date**: 06/12/2019

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, 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

A. Irritable Bowel Syndrome with Diarrhea (IBS-D)

   1. Diagnosis and severity: Fulfill Rome III IBS criteria (see Appendix I).
   2. Other therapies: contraindicated, failed or had significant adverse effect to all the agents below:
      a. Over-the-counter (OTC) Agents (one of each): Fiber/psyllium (not bran), Probiotics.
      b. Prescription Agents (one of each below):
         i. Acute treatment: antispasmodics (dicyclomine, hyoscyamine), antidiarrheals (loperamide)
         ii. Bile Acid sequestrants: cholestyramine, colestipol
         iii. Antidepressants: tricyclic, SSRIs.
   3. Dosage regimen.
      a. Xifaxan (rifaximin): 550mg three times per day for 14 days (#42 tabs per 14 days).

b. Viberzi (eluxadoline):

i. 100mg two times per day.

ii. 75mg two times per day: patients without gall bladder, intolerant to 100mg dose, receiving OATP1B1 inhibitors or has mild to moderate hepatic impairment.

4. Approval

a. Initial: Xifaxan - one course; Viberzi - six months.

b. Re-approval:

i. Reoccurrence or continued symptoms.

ii. Xifaxin – one course; maximum approval to total three courses; Viberzi - one year.

B. *Clostridium difficile* Infections (CDI)

1. Diagnosis and severity

a. Diagnosis.

i. Dificid (fidaxomicin): treatment of diarrhea due to *Clostridium difficile.*

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

b. Lab (must meet at least one below):

i. GDH: positive screen followed by confirmatory test (NAAT or EIA); or

ii. NAAT: positive for toxigenic *C. difficile* but only in patients with documented diarrhea.

c. Zinplava: risk of reoccurrence (two of the risk factors below):

i. Age: ≥65 years.

ii. History of CDI within the previous six months.

iii. Immunocompromised.

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

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

2. Other therapies: contraindicated, failed or had significant adverse effects (See Appendix IV)

a. Dificid (fidaxomicin):

i. Mild to moderate disease: vancomycin (oral).

ii. Recurrent Disease: vancomycin (oral).

b. Zinplava IV (bezlotoxumab):

i. Severe and complicated disease: vancomycin (oral and rectal) plus metronidazole IV.

3. Dosage regimen/approval

a. Initial:

i. Dificid (fidaxomicin): 200mg two times per day for 10 days.

ii. Zinplava IV (bezlotoxumab): 10mg/Kg for one dose.

b. Reapproval: Vancomycin for 10 days prior to reapproval of Dificid.

C. Hepatic Encephalopathy (HE) – criteria for use of Xifaxan (rifaximin).

1. Diagnosis and severity: (Refer to Appendix II)
    a. Severity: Overt HE (OHE) grade II to IVb.
2. Treatment indications for Overt HE (one below):
    a. Active treatment: spontaneous or precipitated episode of HE.
    b. Secondary prophylaxis: post Overt HE episode.
    c. Primary prophylaxis: prevent those at high risk for an episode of OHE with cirrhosis.
3. Other therapies: contraindicated, failed or significant adverse effects (both below):
    a. Lactulose
        i. First choice for treatment of episodic OHE; prevention of recurrent episodes of HE.
        ii. Dose: 25mL every one to two hours until at least two soft, loose stools per day, then maintain at two to three stools per day.
    b. Neomycin.
4. Dosage regimen for approval
    a. Must be in combination therapy with lactulose (no Xifaxan mono-therapy)
    b. Dose: Xifaxan 550mg two times daily.
5. Approval duration.
    a. Initial: six months.
    b. Re-approval: six months.
    c. Discontinue: precipitating factors controlled; or liver function or nutritional status improved.

D. Traveler's Diarrhea – criteria for use of Xifaxan (rifaximin).

1. Diagnosis and severity
    a. Symptoms: mild cramps/urgent loose stools to severe abdominal pain, fever, vomiting and bloody diarrhea.
    b. Onset: six to 48 hours incubation for bacterial and viral pathogens.
    c. Travel in high-risk areas: Asia, Middle East, Africa, Mexico and Central/South America.
2. Other therapies: contraindicated, failed or had significant adverse effects (both below):
    a. Anti-motility agents: loperamide, diphenoxylate.
    b. Antibiotics:
        i. Ciprofloxacin/levofloxacin: 1-day treatment.
        ii. Microbial resistance (*Campylobacter, Shigella, Salmonella*): azithromycin 1000mg times one dose or 500mg per day for one to three days.
3. Dosage regimen
    a. Confirmed diagnosis of *E. coli.*
    b. Xifaxan (rifaximin oral): 200 mg three times per day for three days.

4. Approval
    a. Initial: 1 course - #9 tabs per three days.

**4.0 Coding:**

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

**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, Viberzi, Zinplava, Dificid accessed June 2019.
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.


**7.0 Appendices:**

Appendix I: Rome III criteria – IBS

| Symptoms | | |
|---|---|---|
| Recurrent abdominal pain or discomfort with 2 of the following: | | |
| Improvement with defecation | and/or<br>Onset associated with a change in frequency of stool | and/or<br>Onset associated with a change in form (appearance of stool) |
| Timing | | |
| Onset | Frequency | Symptom Occurrence |
| 6 months prior | 3 days/month | Last 3 months |

Appendix II: HE Description and clinical example

| Type | Grade | | Time Course | Spontaneous or Precipitated |
|---|---|---|---|---|
| A<br>---------- | MHE<br>1 | Covert | Episodic<br>---------- | Spontaneous |
| B<br>----------<br>C | 2<br>3<br>4 | Overt | Recurrent<br>----------<br>Persistent | Precipitated |

*HE patient characterized by 1 component from each of the 4 columns. Example: HE, Type C, Grade 3, Recurrent, Precipitated (by UTI). May be supplemented with operative classifications (e.g. Glasgow Coma Score or psychometric performance.*

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

| Drug | Adverse Reactions | Monitoring | REMS |
|---|---|---|---|
| Xifaxan<br>rifaximin | • CNS: HA<br>• Pregnancy category C | • CNS: mental status changes (HE)<br>• GU: blood in stool<br>• Other: temperature, hypersensitivity reaction | None needed |
| Viberzi<br>eluxadoline | • GI: constipation (7-8%), nausea (7-8%), abdominal pain (6-7%)<br>• Pregnancy: teratogenicity not seen in animal studies | • CNS: cognitive/physical impairment in patient with ↓hepatic function<br>• GI: ↑ abdominal pain with/without nausea, vomiting, and acute biliary pain with hepatic/pancreatic enzymes | None needed |
| Zinplava<br>Bezlotoxumab | • CV: exacerbation of heart failure (13%)<br>• Pregnancy: animal reproduction studies not done. monoclonal antibodies pass through the placenta | • None listed | None needed |

Appendix IV

**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.

## 8.0 Revision History:

Original Effective Date: August 26, 2015

Last Approval Date: 06/12/2019

Next Review Date: 06/12/2020

| Revision Date | Reason for Revision |
|---|---|
| 2/19 | Transitioned to new format |
| | |