DRUG DETERMINATION POLICY

Title: DDP-04 Miscellaneous Gastrointestinal (GI) Agents

Effective Date: 03/17/2020

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. Xifaxan (rifaximin) and Viberzi (eluxadoline).

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

a. Diagnosis and severity: fulfill Rome III IBS criteria (see Appendix I).

b. Other therapies: contraindicated, failed or had significant adverse effects (all below):

i. Over-the-counter agents (one of each below):

1) Fiber/psyllium (not bran).

2) Probiotics.

ii. Prescription agents (one of each below):

1) Antispasmodics: dicyclomine, hyoscyamine.

2) Antidiarrheals

3) Antidepressants: tricyclic, selective serotonin reuptake inhibitors (SSRI)s.

c. Dosage regimen.

i. Xifaxan (rifaximin): 550mg three times per day for 14 days (#42 tabs per 14 days).

ii. Viberzi (eluxadoline): 100mg two times daily (may decrease to 75mg twice daily).

d. Approval.

i. Initial:

1) Xifaxan: one course.

2) Viberzi: six months.

ii. Re-approval: reoccurrence or continued symptoms.

1) Xifaxin: one course (maximum approval to total of three courses).

2) Viberzi: one year.

B. Xifaxin

1. Traveler's Diarrhea.

a. Diagnosis and severity (all below):

i. Symptoms: mild cramps/urgent loose stools to severe abdominal pain, fever, vomiting and bloody diarrhea.

ii. Onset: six hours to two days incubation for bacterial and viral pathogens.

iii. Travel in high-risk areas: Asia, Middle East, Africa, Mexico and Central/South America.

b. Other therapies: contraindicated, failed or had significant adverse effects (must meet both below):

i. Anti-motility agents: loperamide, diphenoxylate.

ii. Antibiotics (one below):

1) Ciprofloxacin/levofloxacin: one day treatment.

2) Microbial resistance (*Campylobacter, Shigella, Salmonella*): azithromycin 1000mg times one dose or 500mg daily for one to three days.

c. Dosage regimen.

i. Confirmed diagnosis of *E. coli.*

ii. Xifaxan (rifaximin oral): 200 mg three times daily for three days.

d. Approval:

i. Initial and repeat episodes: nine tabs per three days (one course).

2. Hepatic Encephalopathy (HE).

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

i. Severity: Overt HE grade II to IVb.

b. Treatment indications for Overt HE (one below):

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

ii. Secondary prophylaxis: post Overt HE episode.

iii. Primary prophylaxis: prevent those at high risk for an episode of OHE with cirrhosis.

c. Other therapies: contraindicated, failed or significant adverse effects:

i. Lactulose, dose titrated to up to three stools per day.

d. Dosage regimen for approval:

i. Must be in combination therapy with lactulose (no Xifaxan mono-therapy).

ii. Dose: Xifaxan 550mg two times daily.

e. Approval duration.

i. Initial: six months.

ii. Re-approval: six months.

iii. Discontinue: precipitating factors controlled; improved liver function or nutritional status

C. Dificid oral (fidaxomicin) and Zinplava IV (bezlotoxumab).

1. *Clostridium difficile* Infections (CDI).

a. Diagnosis and severity.

i. Diagnosis.

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

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

ii. Lab (one below):

1) Glutamate dehydrogenase (GDH): positive screen followed by confirmatory test (nucleic acid amplification test (NAAT) or enzyme-linked immunosorbent assay (EIA)); or

2) NAAT: positive for toxigenic *C. difficile* in patients with documented diarrhea.

iii. Zinplava: risk of reoccurrence (two below):

1) Age: at least 65 years.

2) History of CDI within the previous six months.

3) Immunocompromised.

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

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

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

i. Dificid (fidaxomicin) (must meet below):

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

ii. Zinplava IV (bezlotoxumab) (must meet below):

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

iii. Dosage regimen/approval.

1) Initial:

- Dificid (fidaxomicin): 200mg two times daily for ten days.
- Zinplava IV (bezlotoxumab): 10mg/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, Viberzi, Zinplava, Dificid accessed December 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 Onset associated with a change in frequency of stool	and/or Onset associated with a change in form (appearance of stool)
Timing		
Onset	Frequency	Symptom Occurrence
6 months prior	3 days a month	Last 3 months

Appendix II: HE Description and clinical example

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

Drug	Adverse Reactions	Monitoring	REMS
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

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

Next Review Date: 03/17/2021

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.