Pharmacy Benefit Determination Policy

| | | | |
|---|---|---|---|
| **Policy Subject:** | Miscellaneous GI Agents | **Dates:** | |
| **Policy Number:** | SHS PBD50 | **Effective Date:** | August 26, 2015 |
| **Category**: | Gastroenterology | **Revision Date** | November 5, 2018 |
| **Policy Type:** ☒ **Medical** ☒ **Pharmacy** | | **Approval Date:** | February 28, 2018 |
| **Department:** | Pharmacy | **Next Review Date:** | February 2019 |

| | |
|---|---|
| **Product** (check all that apply): | **Clinical Approval By:** |
| ☒ Group HMO/POS | **Medical Directors** |
| ☒ Individual HMO/POS | PHP: Peter Graham, MD |
| ☒ PPO | **Pharmacy and Therapeutics Committee** |
| ☒ ASO | PHP: Peter Graham, MD |

## Policy Statement:

Physicians Health Plan, PHP Insurance & Service Company, and Sparrow PHP will cover Xifaxan, Viberzi, Dificid and Zinplava through the Medical/Pharmacy Benefit based on approval by the Clinical Pharmacist or Medical Director using the following determination guidelines

## Drugs and Applicable Coding:

**J-code:**

## 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. OTC Agents (1 of each): Fiber/psyllium (not bran), Probiotics
      b. Prescription Agents (1 of each below)
         - Antispasmodics: such as dicyclomine (Bentyl), hyoscyamine (Levsin)
         - Antidepressants: Tricyclic, SSRI's
   3. Dosage regimen
      a. Xifaxan po (rifaximin): 550mg 3x/day x 14 days (#42 tabs/14 days), may repeat regimen twice (total of 3 courses) for re-occurrence
      b. Viberzi po (eluxadoline):
         - 100mg 2x/day
         - 75mg 2x/day: patients without gall bladder, intolerant to 100mg dose, receiving OATP1B1 inhibitors or has mild-mod hepatic impairment
   4. Approval
      a. Initial: Xifaxan - 1 course; Viberzi - 6 months
      b. Re-approval:
         - Re-occurrence or continued symptoms
         - Xifaxin - 1 course; Viberzi - 1 year

B. *Clostridium Difficile* Infections (CDI)
1. Diagnosis and severity
a. Diagnosis
- Dificid po (fidaxomicin): Treatment of diarrhea due to *Clostridium difficile*
- Zinplava IV (bezlotoxumab): Adjunct with antibiotic(s) to decrease recurrence in high-risk patients

b. Lab (1 below)
- GDH: Positive screen followed by confirmatory test (NAAT or EIA) or
- NAAT: Positive for toxigenic *C. difficile* but only in patients with documented diarrhea

c. Zinplava: Risk of reoccurrence (2 of the risk factors below)
- Age: ≥65 years
- History of CDI within the previous 6 months.
- Immunocompromised
- CDI with hyper-virulent strain: ribo-types 027, 078, 244
- 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 po (fidaxomicin):
- Mild-moderate disease: Vancomycin po
- Recurrent Disease: Vancomycin po

b. Zinplava IV (bezlotoxumab):
- Severe and complicated disease: Vancomycin (PO and rectal) + Metronidazole IV

4. Dosage regimen/Approval
a. Initial:
- Dificid po (fidaxomicin): 200mg 2x/day x 10 days
- Zinplava IV (bezlotoxumab): 10mg/Kg x 1

b. Reapprove: Vancomycin x 10 days prior to reapproval

C. Hepatic Encephalopathy (HE)
1. Diagnosis and severity: (Refer to Appendix I)
a. Severity: Overt HE (OHE) grade II-IVb.
b. Blood ammonia
- Increased level alone does not add diagnostic, staging or prognostic value
- Normal levels call for diagnostic re-evaluation

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: Failed or significant adverse effects (both of the below)
a. Lactulose
- First choice for treatment of episodic OHE; prevention of recurrent episodes of HE
- Dose: 25mL every 1-2 hours until ≥ 2 soft/loose BMs/day, then maintain at 2-3 BMs/day

b. Neomycin

4. Dosage regimen
a. Combination therapy with lactulose: No solid data to support Rifaxan use alone
b. Dose: 550mg 2x daily

5. Approval
a. Initial: 6 months.
b. Re-approval: 6 months.
c. Discontinue: Precipitating factors controlled; or liver function or nutritional status improved

D. Traveler's Diarrhea
   1. Diagnosis and severity
      a. Symptoms: Mild cramps/urgent loose stools to severe abdominal pain, fever, vomiting and bloody diarrhea.
      b. Onset: 6-48 hrs. 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:
         - Ciprofloxacin/levofloxacin: 1-day treatment
         - Microbial resistance (*campylobacter, Shigella, Salmonella*): Azithromycin 1000mg x1 or 500mg/day for 1-3 days
   3. Dosage regimen
      a. Only effective for noninvasive *E Coli*
      b. Xifaxan (rifaximin oral): 200mg 3x/day x 3 days
   4. Approval
      a. Initial: 1 course - #9 tabs per 3 days

Appendix I: Rome III criteria – IBS

| Symptoms | | |
|---|---|---|
| Recurrent abdominal pain or discomfort with 2 of the following: | | |
| Improvement w defecation | and/or<br>Onset associated w a change in frequency of stool | and/or<br>Onset associated w 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 & 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 w 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 rifaximin | • CNS: HA<br>• Pregnancy category C | • CNS: Mental Status changes (HE)<br>• GU: Blood in stool<br>• Other: Temperature, hypersensitivity Rx | None needed |
| Viberzi 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 w ↓hepatic fx<br>• GI: ↑ abdominal pain w/wo N & V & acute biliary pain w hepatic/pancreatic enzymes | None needed |
| Zinplava Bezlotoxu-mab | • CV: Exacerbation of heart failure (13%)<br>• Pregnancy: Animal reproduce-tion studies not done. Monoclonal antibodies pass thru 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 ≤15000 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 ≥15000 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.

## References and Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Xifaxan, Viberzi, Zinplava, Dificid accessed Jan. 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. Clinical Practice Guidelines for C. difficile infections in adults and children: 2017 Update by the IDSA and SHEA. CID 2018:66;e1-e48
8. Bezlotoxumab for Prevention of recurrent *C. difficile* infection. N Eng J Med 2017:376(4);305-317.

Pharmacy Benefit Determination Policy

| **Approved By:** | |
|---|---|
|  | 2/28/18 |
| Peter Graham, MD – PHP Executive Medical Director | Date |
|  | 2/28/18 |
| Kurt Batteen - Human Resources | Date |