

MTF Formulary Management for Gastrointestinal-2 (GI-2) Miscellaneous Drugs

Defense Health Agency Pharmacy Operations Division

Bottom Line and What's New since November 2012

- All GI-2 miscellaneous drugs are designated with formulary status on the Uniform Formulary. Metronidazole 250 mg and 500 mg remain on the Basic Core Formulary (BCF).
- Prior Authorization applies to rifaximin for hepatic encephalopathy and traveler's diarrhea. Non-FDA approved uses of rifaximin are not covered.
- Rifaximin 550 mg:
 - The new FDA-approved indication for diarrhea-predominant irritable bowel syndrome (IBS-D) is approved for new users. Prior Authorization (PA) criteria and quantity limits apply (see PA section, below).
 - Note: New rifaximin users for IBS-D are allowed a total of 3 x 14 days courses of therapy in six months.

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the November 2015 DoD P&T Committee meeting on January 29, 2016, with an implementation date of March 30, 2016 (for the rifaximin Prior Authorization update).

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
<ul style="list-style-type: none"> • Metronidazole 250 mg, 500 mg (Flagyl, generics) 	<ul style="list-style-type: none"> • Alosetron (Lotronex; generics) • Fidaxomicin (Dificid)* • Linaclotide (Linzess) • Lubiprostone (Amitiza) • Metronidazole 375 mg, 750 mg ER (Flagyl, Flagyl ER, generics) • Neomycin (Neo-Fradin, generics) • Nitazoxanide (Alinia) • Rifaximin (Xifaxan) • Tegaserod (Zelnorm) – discontinued • Vancomycin 125 mg, 250 mg (Vancocin, generics) 	None
<p>*Dificid is not compliant with the Trade Agreements Act (TAA) and is not available at the MTFs.</p>		

Clinical Summary

Irritable Bowel Syndrome (IBS)

- There are no head-to-head studies among any of the drugs in the GI-2 Miscellaneous Drug Class for treating IBS-D, constipation-predominant IBS (IBS-C), or chronic idiopathic constipation (CIC). Treatment for opioid-induced constipation was not a focus of the review.
- Guidelines recommend choosing a single or combination medication based on the predominant IBS symptom. Antispasmodic agents along with dietary and lifestyle advice should be offered to patients for treating IBS symptoms.

Diarrhea-Predominant IBS (IBS-D)

- **Rifaximin (Xifaxan)** (See Prior Authorization information, below.)
 - The rifaximin studies for IBS-D are of moderate quality evidence.
 - FDA-approval for IBS-D was based on the unpublished TARGET 3 trial, which found that rifaximin was modestly more effective than placebo in relieving IBS-D symptoms, but relapses were common.
 - Rifaximin primarily relieves abdominal pain, but did not show a statistically significant improvement in stool consistency.
 - Rifaximin is generally well tolerated. It is also approved for traveler's diarrhea and to reduce the recurrence of hepatic encephalopathy.

- **Alosetron (Lotronex)**
 - Alosetron is associated with severe adverse events (AEs), including death due to bowel obstruction. Use is restricted to women with severe refractory IBS-D and is only available under an FDA-mandated REMS program.

Constipation-Predominant IBS (IBS-C)

- **Linaclotide (Linzess)**
 - Studies with linaclotide are considered high quality evidence.
 - Linaclotide showed statistically significant improvements in both abdominal pain and an increase in number of bowel movements per week in the two placebo-controlled clinical trials used to obtain FDA approval.
 - Linaclotide has no known drug interactions and is generally well tolerated, although patients may experience diarrhea.
- **Lubiprostone (Amitiza)**
 - Studies with lubiprostone are of moderate quality evidence and were conducted in primarily Caucasian women.
 - Lubiprostone was studied in two placebo-controlled trials and showed varying effects on IBS-C symptoms.
 - The most common AEs with linaclotide are nausea, headache, and diarrhea/abdominal pain. Limitations to the use of lubiprostone (Amitiza) include the drug interaction profile and FDA approval for use only in women for IBS.
- **Tegaserod (Zelnorm)** has been **discontinued** by the manufacturer due to severe AEs, and is only available for compassionate use after application to the FDA.

Chronic Idiopathic Constipation (CIC)

- Linaclotide (Linzess) and lubiprostone (Amitiza) are approved for treating CIC. Both drugs have shown increases in the number or frequency of bowel movements per week. No conclusions regarding comparative efficacy between Amitiza and Linzess for treating CIC can be made.

Hepatic Encephalopathy, Traveler's Diarrhea, & *Clostridium difficile*-associated Diarrhea (CDAD)

- There are no changes to the clinical conclusions from the November 2012 meeting. See <http://www.health.mil/PandT>.

Overall Conclusion

- At this time, comparative efficacy statements between the GI-2 miscellaneous drugs cannot be made, due to widely differing mechanisms of action, lack of head-to-head studies, lack of consistent diagnostic criteria, and variable endpoints.
- Although the studies for IBS-D, IBS-C, and CIC showed statistically significant results, it remains to be determined if these results are clinically meaningful due to the high placebo response.

Rifaximin Prior Authorization

- All new users of rifaximin are required to undergo the manual PA process. Different PA criteria apply, based on the dosage and FDA-approved indication.
- Rifaximin prior authorization is not approved for *C. difficile* infection, inflammatory bowel disease, chronic abdominal pain, hepatitis, diabetes, rosacea, and any other non FDA-approved use.
- Rifaximin (Xifaxan) 550 mg tablets:
 - Irritable Bowel Syndrome-Diarrhea Predominant (IBS-D) — added November 2015
 - Patient has clinically documented moderate to severe IBS-diarrhea type, without constipation, and has symptoms of moderate abdominal pain and bloating.
 - AND
 - The patient has had failure, intolerance, or contraindication to at least one antispasmodic agent; e.g., dicyclomine (Bentyl), Librax, hyoscyamine (Levsin), Donnatal, loperamide (Imodium),

AND

- The patient has had failure, intolerance, or contraindication to at least one tricyclic antidepressant (to relieve abdominal pain); e.g., amitriptyline, desipramine, doxepin, imipramine, nortriptyline, protriptyline.
- If yes to the above, then treatment will be approved for a single 14-day course of therapy (550 mg tablets, one tablet three times daily for 14 days).
- **Re-treatment Criteria:** For IBS-D, patients who experience recurrence of symptoms can be retreated up to two more times with the same regimen (total of three treatment courses in 6 months) if the patient has had a positive response to a previous 14-day course of rifaximin.
- Prior authorization expires in 6 months.
- Hepatic Encephalopathy: (No changes from November 2012)
 - Patient is ≥18 years of age
 - Patient has a documented diagnosis of hepatic encephalopathy
 - Prior Authorization does not expire
- Rifaximin (Xifaxan) 200 mg for traveler’s diarrhea: There are no changes to the PA criteria from the November 2012 DoD P&T Committee meeting.

Quantity Limits

- Rifaximin 550 mg for IBS-D: Limited to TID dosing for one 14-day course of therapy
- Rifaximin 200 mg: For traveler’s diarrhea, if prior authorization is approved, 3-day supply, with no refills
- Fidaxomicin: # 20 tablets with no refill, consistent with the product labeling

References

- DoD P&T Committee minutes: <http://www.health.mil/PandT>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.health.mil/formulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: <http://www.health.mil/DoDPTResources>
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil

GI-2 Miscellaneous Drugs Price Comparison at MTF	
Drug	MTF Cost/Month (Nov 2015)
Basic Core Formulary	
Metronidazole 250 mg, 500 mg	\$ Most Cost-Effective
Uniform Formulary	
Neomycin, metronidazole 375 mg & 750 mg	\$ Most Cost-Effective
Lubiprostone (Amitiza)	\$\$ Less Cost-Effective
Linaclotide (Linzess)	\$\$ Less Cost-Effective
Alosetron (Lotronex)	\$\$\$ Less Cost-Effective
Nitazoxanide (Alinia)	\$\$\$ Less Cost-Effective
Rifaximin (Xifaxan)	\$\$\$ Less Cost-Effective
Fidaxomicin (Dificid)	\$\$\$ Less Cost-Effective
Vancomycin (Vancocin)	\$\$\$ Less Cost-Effective
Nonformulary	
None	
Legend:	
\$	= “Most Cost-Effective” represents Rx’s with the <u>lowest cost</u> and/or best clinical efficacy
\$\$	= “Less Cost-Effective” represents <u>higher cost</u> Rx’s with similar clinical efficacy
\$\$\$	= “Less Cost-Effective” represents <u>next higher cost</u> Rx’s with similar clinical efficacy
\$\$\$\$	= “Least Cost-Effective” represents Rx’s with the <u>highest cost</u> with similar clinical efficacy