

## MTF Formulary Management for Gastrointestinal-2 Miscellaneous (GI-2) Drug Class - Opioid-Induced Constipation (OIC) Subclass

Defense Health Agency Pharmacy Operations Division

### Bottom Line

- Naloxegol (Movantik) and naldemedine (Symproic) are the most cost-effective peripherally acting mu-opioid receptor antagonists (PAMORAs), followed by methylnaltrexone (Relistor).
- Consider lifestyle measures and decreasing the dose of the opioid to reduce constipating effects prior to using a PAMORA.
- Prior authorization applies to the PAMORAs, requiring a trial of a stimulant laxative and an osmotic laxative first. For Relistor tablets, a trial of lubiprostone (Amitiza), naloxegol (Movantik), and naldemedine (Symproic) is required.

**Uniform Formulary Decision:** The Director, DHA, approved the recommendations from the May 2018 DoD P&T Committee meeting on August 6, 2018. Implementation will occur by October 10, 2018.

Uniform Formulary (UF) Agents		Nonformulary (NF) Agents
BCF drugs – MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
None*	<ul style="list-style-type: none"> <li>• Naldemedine (Symproic)</li> <li>• Naloxegol (Movantik)</li> </ul>	<ul style="list-style-type: none"> <li>• Methylnaltrexone (Relistor) tablets and injection</li> </ul>
*Metronidazole will continue as the BCF selection for the GI-2 Miscellaneous class; an OIC drug was not added to the BCF.		

### Clinical Summary

- The Opioid-Induced Constipation (OIC) drugs are referred to as peripherally acting mu-opioid receptor antagonists (PAMORAs).
- PAMORAs inhibit the action of opioids in the GI tract, which decreases constipation, but still maintain the analgesic effects from the mu receptors in the central nervous system.
- Professional treatment guidelines recommend lifestyle modifications, increased fluid intake, regular moderate exercise, a high fiber diet, decreasing opioid doses to the minimal effective dose, and a scheduled dose of a stimulant laxative (e.g., bisacodyl, senna) with or without a stool softener (e.g., docusate) as first-line therapies for OIC.
- The evidence for OIC drug efficacy is limited by the lack of a validated minimally clinically important difference in study endpoints, the allowance of concomitant or “rescue” laxative doses, and the short duration of the trials (less than 3 months). Additionally, in the trials leading to FDA approval, there were differing inclusion and exclusion criteria, especially with regard to intensity of opioid dosing.
- Given the varying efficacy endpoints and lack of head-to-head trials, there is insufficient evidence to conclude that one PAMORA is more effective than another or associated with fewer adverse events.
- There is no long-term safety data available with the OIC drugs. The FDA is requiring cardiovascular outcomes trials (CVOTs) for the PAMORAs to evaluate CV mortality, non-fatal myocardial infarction, and stroke. Results from the CVOTs are pending.
- Naloxegol (Movantik) can be crushed and placed down a nasogastric tube and is also dosed once daily. Disadvantages include the requirement for renal and hepatic dosing adjustment and CYP3A4 drug interactions.

- Advantages of naldemedine (Symproic) include once daily dosing and no need for dose titration or dose adjustment in renal dysfunction. Disadvantages include rare cases of rash and hypersensitivity reactions and CYP3A4 drug interactions.
- Methylnaltrexone (Relistor) tablets lack CYP3A4 drug interactions. However, only very limited data is available (one phase III trial).

### Prior Authorization (PA) Criteria

- All new users of Symproic or Movantik must first try both a stimulant laxative (e.g., bisacodyl, senna) and an osmotic laxative (e.g., Miralax, lactulose). Patients are also required to be taking concurrent opioids.
- Other PA criteria include that the patient must not be taking an opioid antagonist (e.g., naloxone, naltrexone) and must not have suspected GI obstruction or be at risk of GI obstruction. Patients must not be on concomitant CYP3A4 inducers (for Symproic and Movantik).
- PA expires after one year and requires yearly renewal. Renewal is allowed if the patient continues on opioids, continues lifestyle modifications (e.g., laxatives), and has shown improvement in constipation.
- For Relistor tablets, a patient must meet the criteria listed above and also have tried and failed Movantik, Symproic, AND Amitiza.
- Relistor subcutaneous injection is only indicated for use in the palliative care setting, and thus PA does not apply to the injectable form.

### 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/PandT> (scroll down to DoD P&T Committee Meeting Schedule)
- 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](mailto:dha.jbsa.pharmacy.list.poduf@mail.mil)
- Opioid-induced constipation: advances and clinical guidance. Ther Adv Chronic Dis. 2016 Mar; 7(2): 121–134, [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772344/pdf/10.1177\\_2040622315627801.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772344/pdf/10.1177_2040622315627801.pdf)

OIC Subclass Price Comparison at MTF	
Drug	MTF Cost (May 2018)
<b>Basic Core Formulary</b>	
N/A	<b>\$</b> = Most Cost-Effective
<b>Uniform Formulary</b>	
Naldemedine (Symproic)	<b>\$\$\$</b> = Less Cost-Effective
Naloxegol (Movantik)	<b>\$\$\$</b> = Less Cost-Effective
<b>Nonformulary</b>	
Methylnaltrexone (Relistor) injection	<b>\$\$\$\$</b> = Least Cost-Effective
Methylnaltrexone (Relistor) tablet	<b>\$\$\$\$</b> = Least Cost-Effective
Legend: <b>\$</b> = "Most Cost-Effective" represents Rx's with the <u>lowest cost</u> and/or best clinical efficacy <b>\$\$</b> = "Less Cost-Effective" represents <u>higher cost</u> Rx's with similar clinical efficacy <b>\$\$\$</b> = "Less Cost-Effective" represents <u>next higher cost</u> Rx's with similar clinical efficacy <b>\$\$\$\$</b> = "Least Cost-Effective" represents Rx's with the <u>highest cost</u> with similar clinical efficacy	