Methylnaltrexone Bromide Subcutaneous Injection and Tablets
Criteria for Use
May 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria

If ANY item below applies, the patient should NOT receive methylnaltrexone subcutaneous injections.

☐ Known or suspected mechanical gastrointestinal obstruction or other condition that may compromise drug action or cause bowel dysfunction (e.g., acute abdomen, ostomy, active diverticulitis, ischemic bowel, etc.)

☐ Placement of peritoneal catheter for chemotherapy or dialysis (not studied)

☐ End-stage renal impairment on dialysis (not studied)

☐ Use of methylnaltrexone solely for *prevention* of opioid-induced constipation or impaction (no supporting evidence).

☐ Use of methylnaltrexone for postoperative ileus (preliminary results showed inefficacy).

☐ Use of methylnaltrexone for constipation that is not opioid-related (not studied)

☐ Concomitant use of other opioid antagonists (potential for increased risks of additive effects and opioid withdrawal)

Inclusion Criteria for Opioid-induced Constipation in Adults with Chronic Noncancer Pain

All of the following criteria must be fulfilled.

☐ Patient has been taking opioids for chronic noncancer pain (including chronic pain related to prior cancer or its treatment) for at least 4 weeks and does not require frequent opioid dose escalation.

☐ A stimulant laxative (e.g., bisacodyl, sennosides; 1-month trial) is medically inadvisable, inadequate, or not tolerated.

☐ MIRALAX-equivalent (twice daily) or other osmotic laxative (e.g., sorbitol, magnesium (Mg) citrate, etc.; 1-month trial) is medically inadvisable, inadequate, or not tolerated.

☐ Naloxegol at optimized, recommended oral dosage for renal function (at least a 1-week trial) is medically inadvisable, inadequate, or not tolerated.

☐ Naldemedine at optimized, recommended oral dosage (at least a 1-week trial), is medically inadvisable, inadequate, or not tolerated.

☐ Lubiprostone at optimized, recommended oral dosage for hepatic function (at least a 1-week trial), is medically inadvisable, inadequate, or not tolerated.

Inclusion Criteria for Opioid-induced Constipation in Patients with Advanced Illness

All of the following criteria must be fulfilled.

☐Prescriber is a VA/VA Community Care palliative care specialist or provider locally designated to prescribe methylnaltrexone.

☐ Patient has advanced illness for which he/she is receiving palliative care in a monitored setting or at home with hospice care.

☐ Patient has opioid-induced constipation and requires PROMPT laxative effects.

☐ An oral and / or rectal stimulant laxative (e.g., bisacodyl, sennoside) in at least usual doses is medically inadvisable (e.g., dysphagia), inadequate, or not tolerated.

☐ An oral osmotic laxative (such as lactulose or PEG 3350 in low doses) in at least usual doses is medically inadvisable (e.g., dysphagia), inadequate, or not tolerated.

Revisions: May 2020 (added revised Supplemental Information). February 2020 (reformatted for Cerner, removed docusate requirement). December 2019 (added prior cancer-related pain). January 2019 (added naldemedine). January 2017 (added tablets), December 2015. Original: March 2010. Contact: Francine Goodman, PharmD, BCPS, National Clinical Pharmacy Program Manager – Formulary. VA Pharmacy Benefits Management Services (10P4P)

Supplemental Information

General treatment considerations for opioid-induced constipation:

- Conventional laxatives on the VA National Formulary are shown in Table 1.

Table 1. VANF Conventional Laxative Regimens

LAXATIVE	FORMULATION	INITIAL DOSE	USUAL DOSE	MAXIMUM DOSE
		(In divided doses, titrated to individual response)		
ONE OF THE FOLLOWING STIMULANT LAXATIVES				
SENNOSIDES	Oral tablet	15 mg once daily	15–50 mg once or twice daily	70–100 mg in two divided doses
BISACODYL	Oral tablet	5 mg every 2–3 days	5–15 mg every 2–3 days	30 mg every 2–3 days
	Rectal suppository	10 mg every 2–3 days	10 mg every 2–3 days	10 mg every 2–3 days
PLUS ONE OF THE FOLLOWING OSMOTIC LAXATIVES				
LACTULOSE	Syrup	10 g (15 ml) once daily	10–20 g / day (15–30 ml / day) in 1–2 divided doses	60 ml / day in 1–2 divided doses
PEG 3350	Powder for solution, oral	17 g (about 1 heaping Tbsp) of powder mixed in 4–8 oz of water, juice, cola, or tea once daily for not longer than 2 weeks (OTC labeling). The OTC product labeling gives no limit on how frequently a course may be repeated. Under medical supervision, if the laxative response is insufficient, the dose may be increased to twice daily (off-label). Daily use (17 g/d) for constipation has been shown to be generally safe in otherwise healthy adults for up to one year.†		
MAY ADD STOOL SOFTENER FOR SELECTED PATIENTS*				
DOCUSATE	Oral Capsule or Solution	50 mg once daily	50–360 mg in 1–4 divided doses	500 mg in 1–4 divided doses
	Rectal enema	Add 50-100 mg of docusate liquid (not syrup) to enema fluid (saline or water)		

OTC, Over-the-counter. † Center for Drug Evaluation and Research. MiraLax (Polyethylene Glycol 3350) Powder FDA Medical Review, 2006.

* Do not recommend docusate as monotherapy or as the primary therapy for prevention or treatment of opioid-induced constipation. Docusate is relatively safe but low-quality, consistent evidence shows that it is ineffective for opioid-induced constipation and chronic constipation. Clinical practice guidelines (AGA2019-OIC[1] and ESMO2018-Advanced Disease[2]) do not recommend docusate for opioid-induced constipation or constipation in advanced disease.

- Bulk forming laxatives are relatively contraindicated in opioid-induced constipation.
- A stool softener (e.g., docusate) is considered to be of no benefit and low harm for opioid-induced constipation and may be used but is not required prior to use of methylnaltrexone for opioid-induced constipation.
- Orally administered agents naloxegol, lubiprostone, and methylnaltrexone (tablets) may be preferred before daily methylnaltrexone injections.

Treatment of opioid-induced constipation in adults with chronic noncancer pain:

- ***Use of laxatives after initiation of methylnaltrexone therapy:*** Although maintenance laxative therapy should be discontinued before starting methylnaltrexone, laxative(s) can be used as needed if there is a suboptimal response to methylnaltrexone after 3 days.
- Sustained exposure to opioids prior to starting methylnaltrexone may increase the patient's sensitivity to the effects of methylnaltrexone.
- Methylnaltrexone therapy was associated with adverse events that may have been symptoms of opioid withdrawal. These symptoms included abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor and chills.

Treatment of opioid-induced constipation in patients with advanced illness:

- Use of methylnaltrexone subcutaneous injections beyond 4 months has not been studied in the advanced-illness population.
- Opioid-induced constipation in patients with advanced illness may be defined as either fewer than three bowel movements in the preceding week or no bowel movement for 2 days.
- Chronic daily stimulant-based laxative regimens should be continued and optimized in addition to using methylnaltrexone as needed.
- The efficacy of methylnaltrexone was shown when it was added on to usual two- to three-drug laxative therapy.

[1] Crockett S, Greer KB, Sultan S. Opioid-Induced Constipation (OIC) Guideline. *Gastroenterology*. 2019;156(1):228. *Diagram and technical review.* Crockett SD, Greer KB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218–226.

[2] Larkin PJ, Cherny NI, La Carpia D, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29(Suppl 4):iv111–iv125.