

Relistor (Methylnaltrexone) STEPS

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Recommendation:

Due to expense and the availability of many other less expensive, effective agents, methylnaltrexone is not recommended for the inpatient formulary at this time.

Methylnaltrexone was approved by the FDA in April 2008 to treat opioid-induced constipation in palliative patients. Methylnaltrexone is a peripherally acting opioid antagonist that does not cross the blood-brain barrier. It stimulates laxation without reducing the pain relieving effects of opioids or inducing opioid withdrawal.

Safety: -/=

- ❑ **Drug Interactions:** Weak inhibitor of CYP2D6. No clinically significant drug interactions identified.
- ❑ **Renal Impairment:** No dose adjustment is required in patients with mild or moderate renal impairment. Dose-reduction by one-half is recommended in patients with severe renal impairment (CrCl < 30ml/min). No studies were performed in patients with end-stage renal impairment requiring dialysis.
- ❑ **Hepatic Impairment:** No dose adjustment is required for patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone has not been studied.
- ❑ **Elderly:** No difference in efficacy or safety in elderly patients compared to younger patients. No dose adjustment is recommended based on age.
- ❑ **Pediatrics:** Safety and effectiveness has not been established
- ❑ **Pregnancy/lactation:** Category B. Methylnaltrexone is excreted in the milk of lactating rats, but it is not known whether it is excreted in human milk.
- ❑ **Contraindications:** Patients with known or suspected mechanical gastrointestinal obstruction.
- ❑ **Warnings/precautions:** Discontinue in patients who experience severe or persistent diarrhea
- ❑ Increased cardiovascular events have occurred with alvimopan (Entereg), a peripherally acting opioid antagonist. This has not been seen with methylnaltrexone.

Tolerability: =

- ❑ The most common adverse reactions with methylnaltrexone are abdominal pain (28.5%), flatulence (13.3%), nausea (11.5%), dizziness (7.3%), and diarrhea (5.5%)

Efficacy: =/-

- ❑ **Indications:** The treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use for greater than four months has not been studied. It is currently being studied for prevention of post-operative ileus.
- ❑ **Clinical studies:** Approval by the FDA was based entirely on two phase 3 industry sponsored studies. Median age was 68 years. Life expectancy was less than six months. Patients had received opioids for two or more weeks and had received stable doses of opioids and laxatives for three or more days. Median daily baseline oral morphine equivalent dose was 172mg. Opioid induced constipation was defined as either < 3 bowel movements in the preceding week or no bowel movement for > 2days. Patients maintained their regular laxative regimen for at least 3 days prior to study entry and throughout the study.

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Randomized, controlled trial (n=134). Patients received 0.15mg/kg methylnaltrexone or placebo every day for 2 weeks. The baseline use of laxatives was generally comparable across both treatment groups.

Examples of Laxatives Used at Baseline and during Treatment

	Placebo (n = 71)	Relistor 0.15mg/kg (n= 63)
Mean number of laxatives	2.7 ± 1.32	2.5 ± 1.35
Median number of laxatives	3	2
Types of laxatives		
• Bulk	3 (4.2%)	1 (1.6%)
• Contact (bisacodyl, docusate, senna)	58 (81.7%)	51 (81.0%)
• Enemas (sorbitol, sodium phosphate dibasic)	10 (14.1%)	8 (12.7%)
• Magnesium citrate	2 (2.8%)	2 (3.2%)
• Magnesium hydroxide	20 (28.2%)	10 (15.9%)
• Osmotic (PEG, lactulose, magnesium sulfate)	24 (33.8%)	19 (30.2%)
• Softeners (docusate, oil)	28 (39.4%)	26 (41.3%)

In the methylnaltrexone group, 48% of patients had laxation within 4 hours after the first study dose, as compared to 15% in placebo group. 52% had laxation without the use of a rescue laxative within 4 hours after two or more of the first four doses, compared to 8% in the placebo group (p<0.001 for both comparisons)

Relistor (methylnaltrexone) package insert

This study (n=154) compared a single, double-blind, subcutaneous dose of Relistor 0.15mg/kg or Relistor 0.3mg/kg versus placebo. Throughout the study period, patients maintained their regular laxative regimen. Routine use of laxatives was comparable across all treatment groups.

Summary of Routine Laxative Use during Treatment

	Placebo (n = 52)	Relistor 0.15mg/kg (n=47)	Relistor 0.30mg/kg (n = 55)
Mean number of laxatives	2.1 ± 1.25	1.9 ± 1.12	2.0 ± 1.52
Types of laxatives			
• Bulk	2 (3.8%)	0 (0%)	0 (0%)
• Contact (bisacodyl, senna)	37 (71.2%)	29 (61.7%)	37 (67.3%)
• Enemas (sorbitol)	0 (0%)	0 (0%)	2 (3.6%)
• Magnesium citrate	1 (1.9%)	0 (0%)	0 (0%)
• Magnesium hydroxide	2 (3.8%)	1 (2.1%)	1 (1.8%)
• Osmotic (PEG, lactulose)	9 (17.3%)	6 (12.8%)	11 (20.0%)
• Softeners (docusate)	11 (21.2%)	14 (29.8)	9 (16.4)
• Serotonin (Tegaserod)	0 (0%)	0 (0%)	1 (1.8%)

Relistor-treated patients had a significantly higher rate of laxation within 4 hours (62% for 0.15mg/kg and 58% for 0.3mg/kg) than did the placebo treated patients (14%) p<0.0001.

Price: -

Usual Dosage	Dosage Forms	Acquisition price/dose
Relistor 8-12mg SQ q48h	12mg/0.6ml vial (single use)	\$\$\$
	Kits (7 trays per kit, each tray contains one 12mg/0.6ml single use vial, one 1ml syringe with retractable 27 ½ gauge needle, two alcohol swabs)	\$\$\$ (per tray) \$\$\$ x7 (per kit)
Entereg 12mg bid*	12mg caps	\$\$\$\$\$\$\$ (\$\$\$ x4 per day)

*Opioid-induced constipation is an off-label use. This is the dose for postoperative ileus prophylaxis

Simplicity: -

Administered as a SQ injection given once every other day. No more than one dose should be given in a 24-hour period. The dose is 8mg for patients who weigh between 38kg and 61kg. The dose is 12mg for patients who weigh between 62kg and 114kg. Patients outside of those weight ranges should be given 0.15mg/kg. In approximately 30% of patients, laxation was reported within 30 minutes so patients should be advised to be within close proximity of toilet facilities. The drug should be discontinued if the opioid pain medication is discontinued. Relistor is to be injected in the skin of the upper arm, abdomen, or thigh. Vials are stored at room temperature. Drug is to be used within 24 hours once it is drawn up into a syringe. Package insert contains detailed instructions for patients regarding subcutaneous injection procedures.