



## Therapeutic Class Review<sup>SM</sup>

### Gastrointestinal – methylnaltrexone (Relistor<sup>TM</sup>)

October 2008

**New Product for Review:**

methylnaltrexone (Relistor<sup>TM</sup>) [Wyeth]

**Dossier Provided by Manufacturer: Yes**

**Dossier Evaluation: 3**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

**Executive Summary**

*Opioid-induced constipation:*

- Constipation is the most common adverse effect of chronic opioid therapy and one to which few patients develop tolerance.
- Prevention of constipation is the best strategy and helps prevent non-compliance with chronic opioid treatment.

*Management of opioid-induced constipation:*

- A scheduled regimen of laxatives is recommended for patients prescribed long-term opioids to help prevent opioid-induced constipation.
- There are many pharmacologic options for the management of opioid-induced constipation.
- Standard options include combinations of stool softeners, bowel-stimulating laxatives, and bulk-forming laxatives.
  - **Stool softeners:** docusate, lactulose, magnesium salts, polyethylene glycol, sodium phosphate.
  - **Bowel-stimulating laxatives:** bisacodyl, cascara sagrada, senna.
  - **Bulk-forming laxatives:** psyllium, calcium polycarbophil, methylcellulose.
- Prokinetic agents, such as metoclopramide, have also been used for management of opioid-induced constipation.
- Lowering the dose of narcotic is not a useful management strategy because the dose of narcotic that causes constipation is up to four times lower than the analgesic dose.

*Methylnaltrexone (Relistor):*

- Methylnaltrexone (Relistor) is a selective  $\mu$ -opioid receptor antagonist approved for the treatment of opioid-induced constipation in terminally ill patients (expected survival less than 6 months) who have failed standard laxative options.
- It is given via subcutaneous injection up to every other day as needed.
- Current methylnaltrexone (Relistor) studies are not of sufficient duration to determine its long-term safety or effect on narcotic analgesia.
- Aggressive therapy with standard options is the safest and most cost effective therapy for the management of opioid-induced constipation.
- There is a high potential for off-label use with methylnaltrexone (Relistor).

### **Evidence**

- The evidence from one trial that compared methylnaltrexone (Relistor) with placebo was possibly useful.
  - Efficacy was based on a single-dose.
  - For every two patients who received a single dose of methylnaltrexone (Relistor), one patient achieved a laxation response within four hours.
- The evidence from a two-week trial comparing methylnaltrexone (Relistor) with placebo was not reliable.
  - Efficacy was based on proportion of patients with rescue-free laxation response within 4 hours after two or more of the first four doses of methylnaltrexone (Relistor).
  - A large proportion of non-completers was among the reasons for its appraisal as unreliable.
- The short-duration of the RCTs is not sufficient to establish the lack of long-term effect of methylnaltrexone (Relistor) on opioid analgesia.
- There are no studies that evaluate:
  - The efficacy of methylnaltrexone (Relistor) as compared with standard therapies.
  - The long-term efficacy of methylnaltrexone (Relistor).

### **Decision**

Methylnaltrexone (Relistor) is non-preferred/non-formulary because:

- There are no reliable studies establishing its long-term safety and efficacy.
- There are safe and effective options available.
- There are no studies to show that it is better than standard treatment alternatives.
- There is a high potential for use in populations where chronic use may be a safety concern.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s)	FDA approved indications	Usual Dose/Route	Potential Off-label Uses
methylnaltrexone (Relistor™)	04/2008	04/2013	Opioid-induced constipation in patients with advanced illness who are receiving palliative care, after failing laxative therapy	0.15 mg/kg per dose injected subcutaneously every other day as needed, NTE one dose in a 24-hour period	Opioid-induced constipation outside the palliative setting (any chronic opioid user)
metoclopramide (Reglan®)	06/1989	generic	<ul style="list-style-type: none"> <li>• Chemotherapy-induced nausea and vomiting (prophylaxis)</li> <li>• Diabetic gastroparesis</li> <li>• Gastroesophageal reflux disease</li> <li>• Intestinal (small bowel) intubation</li> <li>• Postoperative nausea and vomiting</li> <li>• Radiography of gastrointestinal tract</li> </ul>	10-15 mg ORALLY up to 4 times daily (30 min before meals and at bedtime)	Hiccoughs, migraine, decreased lactation, indigestion, nondiabetic gastroparesis, pheochromocytoma, vomiting of pregnancy
bisacodyl tab and rectal suppository (Dulcolax®)	OTC	expired	Constipation, preparation of bowel for procedure [bowel stimulant]	10mg/day to 30mg/day	Bowel care (spinal cord injury), gastrointestinal manometry, neurogenic bowel
polyethylene glycol 3350 (Miralax®)	OTC	generic	Constipation [saline laxative]	17g/day	Colonoscopy, chronic constipation, dysfunctional voiding
docusate sodium (Colace®)	OTC	generic	Constipation care [stool softener]	Orally: 50 to 200 mg/day	
Senna extract	OTC	Generic	Short-term treatment of constipation and to evacuate the colon for rectal and bowel examination [bowel stimulant]	Tablet: 15 to 17 milligrams (mg) once a day, up to a maximum of 34 to 50 mg twice a day Syrup: 10 to 15 mL once a day, up to a maximum of 30 mL/day for adults	

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

## References

1. Relistor<sup>®</sup> (methylnaltrexone) prescribing information. Wyeth: Philadelphia, PA; April 2008.
2. Product Dossier: Tekturna<sup>®</sup> (aliskiren). Novartis Pharmaceuticals Corporation: East Hanover, NJ; May 2007.
3. FDA Center for Drug Evaluation and Treatment. Approval package for application number NDA 021964 (methylnaltrexone); Medical Review. Available at: <http://www.fda.gov/cder/foi/nda/2008/021964s000TOC.htm>. Accessed on 7/2008.
4. Meha Patel, Medical Information, Wyeth Pharmaceuticals Inc.
5. Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Eng J Med* 2008; 358:2332-43.
6. McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews* 2008, Issue2. Art.No.: CD006332. DOI: 10.1002/14651858.CD006332.pub2.
7. Goodheart CR, Leavitt SB. Managing opioid-induced constipation in ambulatory-care patients. *Pain Treatment Topics*. Aug 2008.
8. Karen Beauchamp, Regional Account Manager [personal communication]. Wyeth Pharmaceuticals Inc.
9. Entereg<sup>™</sup> (alvimopan) prescribing information. GlaskoSmithKline: Research Triangle Park, NC; May 2008.