CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

METHYLNALTREXONE
(Relistor™ – Wyeth Canada)

Description:
Methylnaltrexone is a mu-opioid receptor antagonist approved by Health Canada for the treatment of opioid-induced constipation in patients with advanced illness receiving palliative care; it may be used as adjunct therapy when response to laxatives has been insufficient.

Dosage Forms:
Supplied as a 20 mg/mL solution for subcutaneous injection with each single use vial containing 12 mg of methylnaltrexone in 0.6 mL of sterile water. The recommended dose is 8 mg to 12 mg, based on body weight, given every other day as needed.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that methylnaltrexone not be listed.

Reasons for the Recommendation:
1. The evidence for greater effectiveness over other agents is lacking, therefore, the cost effectiveness of methylnaltrexone compared to other laxatives is uncertain. There are no randomized controlled trials (RCTs) comparing methylnaltrexone with other laxatives. The cost of methylnaltrexone is [redacted] per dose, which is greater than that of oral laxatives, suppositories or sodium phosphate enemas.

2. The two RCTs considered by the Committee had trial design features that limited the ability to estimate the effectiveness of methylnaltrexone versus placebo. The study population of the two RCTs considered by the Committee did not represent patients [redacted] and there was no active comparator. The importance of the primary study outcome of both RCTs (rescue-free laxation within four hours) is uncertain relative to the importance of incidence of weekly bowel movements. The incidence of weekly bowel movements, a secondary outcome, was similar in the methylnaltrexone and placebo groups during the second week of the only two week study.

Summary of Committee Considerations:
The Committee considered a systematic review of two double-blind randomized controlled trials evaluating the effects of methylnaltrexone compared to placebo in palliative care patients taking other laxatives (n=287). The study population included many patients who did not report severe constipation at baseline and whose background regimens were not optimized. About one-third of patients in the trials

were receiving only one class of laxative at baseline. One study was a single dose trial and the other was 2 weeks in duration.

Compared to placebo, methylnaltrexone was associated with statistically significant improvements in the proportion of patients with rescue-free laxation within four hours, the time to laxation and the number of rescue-free laxations during the first week. Methylnaltrexone showed some improvements compared to placebo for the patient global impression of change and clinician global impressions of change scales, however, the scales used in the trials have not been validated. There were no statistically significant differences between methylnaltrexone and placebo in the use of rescue therapies, enemas or disimpaction. The incidence of weekly bowel movements was similar in the methylnaltrexone and placebo groups during the second week of one study. Quality of life was not assessed in either study.

The incidence of abdominal pain was higher in patients taking methylnaltrexone compared to placebo; this was statistically significant in one study (methylnaltrexone: 32 to 44%, placebo: 6%). However, there was no difference in rates of withdrawal due to adverse events between the methylnaltrexone and placebo groups. There were no statistically significant differences between methylnaltrexone and placebo in the rates of other adverse events.

There were no active comparators in the trials, therefore, there is no evidence that methylnaltrexone is superior to other less expensive treatments. The cost of methylnaltrexone is [redacted] per dose, which is greater than that of oral laxatives (e.g. senna, docusate, lactulose each cost less than $1 per day) or sodium phosphate enemas ($3.26 per dose).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. The Committee considered the effectiveness of methylnaltrexone in the subgroup of patients who reported “quite a bit” or “very much” constipation-related distress at baseline. It was not possible to draw conclusions about patients with severe constipation due to the post-hoc nature of this analysis, small sample size, and because the trial excluded patients with faecal impaction.

3. While there are potential advantages of a laxative agent that can be administered subcutaneously, the Committee had concerns regarding the potential for off-label use and overuse of methylnaltrexone.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication’s effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.