PUBLIC SUMMARY DOCUMENT
Product: Methylnaltrexone bromide, injection, 12 mg in 0.6 mL (base), Relistor®
Sponsor: Wyeth Australia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought an authority required listing in the Palliative Care Section for initial and continuing treatment of opioid-induced constipation in patients who have failed to respond to, or are unable to tolerate laxative therapies.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Methylnaltrexone (MNTX) was TGA registered on 17 November 2008 for 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.

4. Listing Requested and PBAC's View

Authority Required
Opioid-induced constipation. Patients must have failed to respond to, or are unable to tolerate, laxative therapies.

Authority Required
Opioid-induced constipation. Patients must have demonstrated a response to previous doses of methylnaltrexone.

The sponsor, in its pre-Sub-Committee Response, accepted the following amendments to the restriction:
Authority Required
Initial supply for palliative care patients with opioid-induced constipation who have failed to respond to, or are unable to tolerate, laxative therapies.

Continuing supply for palliative care patients with opioid-induced constipation who have demonstrated a response to methylnaltrexone, and where consultation with a palliative care specialist or service has occurred.
NOTE:
No applications for increased repeats will be authorised.

Authority Required
Continuing supply for palliative care patients with opioid-induced constipation who have demonstrated a response to methylnaltrexone.

NOTE:
No applications for increased repeats will be authorised.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Opioids form the mainstay of pain management for patients receiving palliative care. However, opioid therapy is often associated with a range of adverse effects, including opioid-induced constipation (OIC). In patients with cancer, constipation is a common complication and a cause of significant distress. In addition to receiving opioid therapy, palliative care patients are also immobile, may have a diet lacking in fibre and a reduced fluid intake, all of which can contribute to constipation.

Currently the mainstay of OIC management is the use of oral laxatives for symptomatic treatment. Laxatives are usually prescribed upon initiation of opioid therapy, however a proportion of patients become unresponsive to, or are unable to tolerate, oral laxative treatment. Many laxative agents require significant fluid intake, which can be difficult to tolerate for a patient with advanced stage disease. When patients no longer respond to oral laxatives, topical interventions include enemas and suppositories, and manual disimpaction may be required in some patients.

MNTX would provide an alternative treatment for opioid-induced constipation in palliative care patients where the patient cannot tolerate or is not responding to other available treatments.

6. Comparator

The submission nominated placebo as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission was based on two direct randomised controlled trials, comparing methylnaltrexone and placebo:

- MNTX 301 was a multi centre, single dose, randomised, controlled study (either 0.15 mg/kg or 0.30 mg/kg methylnaltrexone vs placebo), followed by a 28 day variable dose, open label period (dose varied at clinician's discretion). MNTX 301 EXT was a 3 month, variable dose, open label extension of MNTX 301 (dose varied at clinician's discretion).
- MNTX 302 was a 14 day, randomised, controlled study (0.15mg/kg methylnaltrexone vs placebo). MNTX 302 EXT was a 3 month, variable dose, open label extension of MNTX 302 (dose varied at clinician's discretion).

The submission is primarily based on MNTX 302.

The trial published at the time of submission is listed below:

Trial ID	Protocol title/ Publication title	Publication citation
MNTX 302 Thomas et al.	Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness	New England Journal of Medicine, 2008: 358: 2332-43

8. Results of Trials

The MNTX 301 trial compared methylnaltrexone 0.15 mg/kg and 0.30 mg/kg to placebo for laxation within 4 hours and 24 hours of a single subcutaneous administration. The MNTX 302 trial compared methylnaltrexone 0.15 mg/kg to placebo for laxation within 4 hours and 24 hours of each of 7 administrations in a 14 day period. All patients continued their usual laxative therapy during the trials. Patients requiring rescue therapies (invasive interventions

such as suppositories, enemas or manual evacuation) to achieve laxation were treated as non-responders.

The trial results of proportion of responders for rescue-free laxation within 4 hours of first dose in trials MNTX 302 and MNTX 301 showed that there were statistically significantly more responders in the methylnaltrexone arms compared to placebo. There was no evidence of an increase in efficacy with the higher dose of methylnaltrexone (0.30 mg/kg) compared to the lower dose (0.15 mg/kg).

The proportion of responders for rescue-free laxation within 4 hours of dose and 24 hours of dose over 7 doses in trial MNTX 302 was consistently greater than in those patients receiving placebo. There was no apparent attenuation of efficacy over 14 days of treatment.

There was no evidence of attenuation of efficacy for methylnaltrexone over the MNTX 302 EXT study period of 3 months, with surviving RCT treatment arm patients maintaining their proportion of responses to treatment and surviving RCT placebo arm patients attaining similar response proportions to those from the treatment arms.

Quality of life was not assessed in either MNTX 302 or MNTX 301 or associated extension studies.

During the randomised placebo controlled trials and extension studies (including the 30 day follow up periods) 56% of patients died in study MNTX 301 and 45% of patients died in study MNTX 302. One death due to dehydration secondary to severe diarrhoea was attributed to methylnaltrexone which occurred when this patient was given the higher dose of 0.30 mg/kg (MNTX 301 open-label study). Dehydration was reported less frequently in the methylnaltrexone group compared to the placebo group in the double-blind study of trial MNTX 302 and there was no statistically significant difference between treatment and placebo groups in reports of diarrhoea ($p = 0.479$).

In trials MNTX 301 and MNTX 302 treatment related adverse events were reported more frequently in the methylnaltrexone groups compared to placebo. However, more severe adverse events were reported in the placebo groups (MNTX 301 = 9.6%, MNTX 302 = 28.2%) compared to the methylnaltrexone groups at a dose of 0.15 mg/kg (MNTX 301 = 4.3%, MNTX 302 = 23.8%). The most frequently reported severe adverse event was neoplasm progression. Adverse events and severe adverse events were more frequent in the open-label extension studies (MNTX 301 = 96.7%, MNTX 302 = 100%) compared to the double-blind studies.

The adverse events reported more frequently in the treatment groups compared to placebo were abdominal pain, flatulence, nausea, vomiting, diarrhoea and dizziness.

9. Clinical Claim

The submission claimed that methylnaltrexone is superior to placebo in terms of comparative effectiveness for the treatment of opioid-induced constipation in palliative care patients and that methylnaltrexone is generally well tolerated with the occurrence of treatment emergent adverse events similar to placebo.

The PBAC accepted this claim, however noted that patients receiving methylnaltrexone reported more adverse events than those receiving placebo due to an increased incidence of gastrointestinal pain and discomfort.

10. Economic Analysis

The submission presented a Markov analysis based on a stepped economic evaluation with a time horizon of 4 months (extrapolated from the 2 week MNTX 302 RCT data) and a cycle length of one day branching to five health states; optimal (laxation within 4 hours), moderate (laxation between 4 and 24 hours), and non-responders (no laxation), dropouts and deaths.

The economic evaluation resulted in a baseline ICER in the range of $15,000 - $45,000 per QALY. The results of the sensitivity analyses indicated that the model was most sensitive to assumptions regarding frequency of dosing, the utility of optimal responders (no constipation), and optimal/moderate responder rates respectively.

The submission derived health related quality of life utility weights for opioid induced constipation from Schmier et al. (2002) and the MNTX 302 trial and extension study data.

For PBAC's comments, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5. This was considered to be an underestimate.

12. Recommendation and Reasons

The PBAC considered that the proposed restriction for methylnaltrexone did not define those patients at highest risk and that any future submission should consider restricting use to a subgroup of patients with high clinical need, such as end stage palliative care patients. The PBAC also considered that treatment should be limited to a maximum period of 4 months, given that the evidence supporting the efficacy and safety of methylnaltrexone is limited to a time horizon of 4 months. Pre-filled syringes should also be available in preference to the vials as this would facilitate ease of use for carers managing patients at home and potentially reduce wastage.

The PBAC noted comments from consumers and acknowledged that opioid-induced constipation (OIC) is a significant problem. The PBAC agreed that methylnaltrexone is an effective medication for OIC. The PBAC considered that the clinical claim that methylnaltrexone is superior to placebo in terms of comparative effectiveness for the treatment of opioid-induced constipation in palliative care patients was reasonable. However, it was noted that patients receiving methylnaltrexone reported more adverse events than those receiving placebo due to an increased incidence of gastrointestinal pain and discomfort.

The PBAC noted that the submission presented a Markov analysis based on a stepped economic evaluation with a time horizon of 4 months (extrapolated from the 2 week MNTX 302 randomised control trial data). This was considered reasonable as the responses seem to be maintained.

However, the PBAC identified 3 main areas of concern in the economic model.

Firstly, the economic model aligns constipation states with response categories to methylnaltrexone from Study MNTX 302 (2 week data) and uses 3 patient groupings (severe constipation equates to laxation in 24 hours; moderate constipation equates to laxation in 4-24 hours; no constipation equates to laxation within 4 hours) and assumes that all patients start in the severe constipation group. However, there is no basis provided to support this alignment of different concepts of health state levels and response categories – it is not likely to be the case that the physical act of laxation relieves all the feelings and symptoms of constipation such as bloating and abdominal discomfort. Further, the PBAC noted that all patients continued their usual laxative therapy during the trials (MNTX 301 and 302). Patients requiring rescue therapies (invasive interventions such as suppositories, enemas or manual evacuation) to achieve laxation were treated as non-responders.

Secondly, the transformation of the mean utility scores for constipation health states derived from Schmier et al. (2002) to weighted utilities for constipation treatment response is not adequately justified in the submission. Again, there is no basis provided to support this alignment of different concepts of health state levels and utilities. The PBAC considered that, overall it was not reasonable to assume that the utility of an optimal treatment responder is the same as the utility of someone without constipation, nor that the utility of a moderate responder is the same as the utility of a person with moderate constipation. The PBAC noted that there is considerable uncertainty associated with these assumptions and the model is sensitive to changes in these utilities.

In this regard, the PBAC further noted that the Schmier study estimated preference weights, which are only interpretable relative to each other, and not in any other context, and not as acceptable QALY weights. It appears that preference weights have been derived from the utility functions estimated based on the choice experiment conducted in the Schmier study, and these have been fitted to a 0-1 scale, but insufficient information about the methods is provided in the original paper and in the submission to explain the methods. If the estimates are the coefficients from the regressions, it should be noted that utility functions estimated from choice experiments are subject to scale effects, and it is not appropriate to interpret this as a cardinal utility function on a 0-1 scale. The tradeoffs considered in this study can only be interpreted relative to each other, eg how many more days of pain to avoid constipation. The PBAC considered that for a preference index to be interpreted as a QALY weight, there needs to be some trade-off of survival and quality of life (QOL) presented in the study from which the estimates are derived – which is not what has been undertaken by the submission because all scenarios are of 2 weeks duration. There is no evidence that the scale is anchored at 0 = death and 1 = full health, and, in the context of the listing sought, the utility increments across the three health states seem implausibly large when considered as the amount of remaining life being traded off for each increment. The PBAC noted that no information is provided on the actual model (type of model, the model specification, what beta parameters were included, any parameters of fit, etc) used to derive these values and that there is no information on the design of the conjoint analysis. In addition the structure of the modelled economic evaluation does not fully capture the two clinically relevant outcomes: laxation within 4 hours (primary outcome in the trials) and more than 24 hours after therapy, both of which are relevant to patients.

The PBAC also considered that there is further uncertainty in the utility estimates due to possible differences in populations (i.e. trials, Schmier and Australian populations) and uncertainty regarding how the adaptive conjoint analysis selected the scenarios to give to

participants. The PBAC noted that, in the methylnaltrexone trials the majority of patients were classified as being WHO performance status of 3 or 4, meaning they were significantly less mobile than the population in the Schmeir study that attended clinics to complete the interviews for the conjoint analysis. In the Schmeir study, only 20% of patients had cancer and this had not necessarily reached a terminal phase. The PBAC considered that the supplementary analysis provided by the sponsor in its Pre-Sub-Committee response did not satisfy the notion that these are now similar populations that would elicit similar responses in valuing their relative health states.

Thirdly, the results of the sensitivity analyses indicate that the model is most sensitive to the frequency of methylnaltrexone dosing, the utility of optimal responders (no constipation), and optimal/moderate responder rates. The PBAC noted that if doses are given on alternate days rather than at the longer intervals (3.8 to 4.3 days) reported in trial MNTX 302 EXT, this produces an ICER in the range of $45,000 - $75,000 /QALY compared to the baseline which was in the range of $15,000 - $45,000. Using the utility of mild constipation in Schmier of 0.64 for the optimal responder utility produces an ICER in the range of $45,000-$75,000/QALY. Varying response rates for optimal and moderate responders by 95% confidence intervals produced an ICER for which the lowest value was in the range of $15,000 - $45,000 and the highest value was in the range of $45,000 - $75,000/QALY for optimal responders and moderate responders. A multi-variate analysis, assuming alternate day administration and an optimal responder utility of 0.64 produces an ICER in the range of $75,000 - $105,000 /QALY. The PBAC considered that given the sensitivity of the model to changes in these utilities, there is considerable uncertainty associated with these estimates.

The PBAC considered that there was significant uncertainty about the size of the eligible population due to variation in the reported incidence of constipation and failure with existing PBS-listed laxative treatments defined as rescue “invasive procedures” (ie suppositories and enemas). The PBAC noted that there was also considerable uncertainty around the uptake of the drug in the eligible population and that there was considerable risk that methylnaltrexone would be used beyond the restricted population (as first line treatment for constipation in the palliative care population and in patients with chronic disabling pain requiring long term opioid therapy).

The PBAC noted that the utilisation estimates were based on the availability of a single strength 12 mg vial which could result in considerable wastage in patients weighing less than 62 kg and that the availability of 8 mg pre-filled syringes could result in cost savings from less wastage.

Therefore, the PBAC rejected the application on the basis of high and uncertain cost-effectiveness.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor’s Comment

Wyeth acknowledges the PBAC comments and will continue to work with the PBAC to ensure a successful listing for the benefit of palliative care patients.