The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**methylNaltrexone (Relistor®)** is accepted for restricted use within NHS Scotland for treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient. It is restricted to use by physicians with expertise in palliative care.

Methylnaltrexone has been shown to be superior to placebo in achieving bowel movement in terminally ill patients with opioid-induced constipation already receiving a stable laxative regimen.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
Indication
Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.

Dosing information
The recommended dose is 8 mg (0.4 ml) by subcutaneous injection (for patients weighing 38-61 kg) or 12 mg (0.6 ml) (for patients weighing 62-114 kg). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg.

The usual schedule is one single dose every other day. Doses may be given with longer intervals, as per clinical need. Patients may receive two consecutive doses 24 hours apart, only when there has been no response (bowel movement) to the dose on the preceding day.

Product availability date
08 July 2008

Summary of evidence on comparative efficacy
Methylnaltrexone bromide is a quaternary derivative of the non-selective opioid antagonist naltrexone. It has lower lipid solubility resulting in restricted access across the blood-brain barrier and therefore it is effective in reversing the peripherally mediated side effects of opioids, without interfering with the desired central analgesic effects. It selectively binds at the peripheral mu-opioid receptor with limited potency at the kappa receptor and much reduced activity at the delta opioid receptor.

There were two pivotal phase III studies, both in patients with advanced medical illness and limited life expectancy, receiving a stable dose of opioid for at least three days prior to randomisation, on a stable laxative regimen for at least three days prior to treatment, and suffering from opioid-induced constipation (defined as no clinically significant bowel movement within 48 hours). Efficacy assessments were similar in both studies and included frequency, consistency, difficulty, and time to defaecation.

In a double-blind, single-dose study to evaluate the efficacy of methylnaltrexone, 154 patients with a life expectancy of between one and six months were randomised to a single administration of either subcutaneous methylnaltrexone 0.15mg/kg (n=47) or 0.30mg/kg (n=55) or placebo (n=52), followed by a 4-month open-label extension period. Treatment with additional laxatives was permitted during the study as clinically indicated, although not permitted within four hours before or after administration of the double-blind dose.

The primary outcome was the proportion of patients with defaecation (without a rescue intervention) within four hours of the first dose. In the methylnaltrexone 0.15mg/kg group, 29 patients (62% (95% confidence interval (CI): 48 to 76)) had a bowel movement within four hours compared with 32 (58% (95% CI: 45 to 71)) methylnaltrexone 0.30mg/kg patients and seven (13% (95% CI: 4 to 23)) placebo patients.

Secondary outcomes included the median time to defaecation and defaecation (without rescue intervention) within 24 hours. The median time to bowel movement for patients in both methylnaltrexone groups was significantly shorter than placebo (1.1 hours and 0.8 hours for the 0.15mg/kg and 0.3mg/kg doses respectively, compared with >24 hours for placebo). Significantly more patients had bowel movement within 24 hours of receiving methylnaltrexone compared with placebo patients (68% and 64% for 0.15 and 0.3mg/kg doses respectively versus 27% for placebo).
In the other, multicentre, double-blind, placebo-controlled study, 134 patients with a life expectancy of at least one month were recruited from nursing homes, palliative care sites or hospices. Patients were randomised to two weeks of double-blind treatment with either methylnaltrexone 0.15mg/kg (n=62) on alternate days (titrating to 0.3mg/kg if required) or placebo (n=71), followed by a 3-month open-label phase. Missing values were imputed from the last observation carried forward.

There were two co-primary endpoints during the double-blind phase: the proportion of patients who had defaecation (without a rescue intervention) within four hours of the first dose and the proportion of patients who had defaecation within four hours after two or more of the first four doses (the first week of double-blind treatment). In the methylnaltrexone group, 30 patients (48% (95%CI: 36 to 61)) had bowel movement within four hours compared with 11 placebo patients (16% (95%CI: 7 to 24)). For the second primary endpoint, 32 methylnaltrexone patients (52% (95% CI: 39 to 64)) compared with six placebo patients (8% (95%CI: 2 to 15)) had bowel movement after two or more doses in the first week of treatment.

Secondary and tertiary outcomes included the proportion of patients with defaecation within four hours after four or more of the seven doses, the proportion of patients with defaecation within four to 24 hours after each dose, the time to bowel movement, overall pain scores and symptoms of opioid withdrawal. These endpoints in general supported the results of the primary outcomes. There were no differences between the groups in pain scores over the study period, indicating that methylnaltrexone did not cause clinically relevant opioid withdrawal symptoms.

There were no defined primary outcomes for the open-label extension and it mainly provided information on the long-term safety of methylnaltrexone. However it did show that the time to defaecation remained fairly constant over time. In an additional analysis, when the outcomes of the first dose of the two studies was combined, age and gender were found not to influence the outcome.

**Summary of evidence on comparative safety**

The overall rate of adverse events was similar in the methylnaltrexone (81%) and placebo groups (80%). In the methylnaltrexone group, the most commonly reported treatment-emergent adverse events were abdominal pain (17%), flatulence (13%), vomiting (13%), nausea (11%), and malignant neoplasm progression (11%). Most treatment-emergent adverse events were rated as mild or moderate by the investigators. In a majority of the patients in both treatment groups, the treatment-emergent adverse events were not related or were unlikely to be related to study drug.

Serious adverse events occurred in 18% of methylnaltrexone patients and 28% of placebo patients, none were deemed by the investigators to be related to study drug. Discontinuations due to adverse events occurred in 6% and 7% of patients in the methylnaltrexone and placebo groups, respectively.
Summary of clinical effectiveness issues

Methylnaltrexone has been shown to be superior to placebo in achieving defaecation (without the need for rescue intervention) in terminally ill patients with opioid-induced constipation, who were already being treated with a stable laxative regimen. A re-analysis of responders requested by the Committee for Medicinal Products for Human Use (CHMP) found that the more severe the constipation, the higher the response with methylnaltrexone. The side effect profile was as expected. However the studies had small patient numbers and the double-blind assessment period was of short duration.

Just over half of patients achieved bowel movement within four hours of the initial dose and this may be due to a number of confounding factors including use of other concomitant medications, the disease process, diet, immobility and lack of fluid intake. In addition, opioids cause decreased gastric emptying and prolonged oral-caecal transit time through a centrally mediated action. These effects would not be inhibited by the peripheral action of methylnaltrexone.

The European Public Assessment Report (EPAR) noted that a reduction in overall ‘usual laxative medication’ was not convincingly shown. There was a significant difference in the proportion of patients who achieved a ‘satisfactory’ weekly bowel movement frequency in the first week but there was no significant difference in this outcome in the second week which might suggest that methylnaltrexone has a similar efficacy to standard and rescue laxative treatment combined.

The primary outcome in the clinical studies investigated methylnaltrexone used as an add-on treatment to already stable laxative therapy, so more of a rescue treatment rather than continuous treatment of constipation aimed at normalisation of bowel movement. Therefore, the single-dose study followed by as needed administration may better reflect the use of methylnaltrexone in clinical practice. For the patients in whom the drug shows efficacy it offers an alternative to the discomfort of an enema or the indignity of a manual evacuation.

Subcutaneous administration rather than an oral formulation and a requirement to rotate the injection site may be potential disadvantages, especially in patients who may already be receiving a number of injections. At present no compatibility studies have been done and therefore methylnaltrexone should not be mixed with other drugs. Most of the patients in the studies were WHO performance status 3 or 4, therefore should represent the patients in whom this will be used in practice. However in the two-week double-blind study, all the recruited patients were in care and therefore may not represent the situation for those patients wishing to self-administer.

The European Medicines Agency (EMEA) has emphasised that methylnaltrexone should not be used in indications outwith its marketing authorisation.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing two treatment sequences in the treatment of opioid-induced constipation in advanced illness palliative care patients who have had an insufficient response to usual laxative therapy. One treatment pathway involved patients using oral laxatives, then enemas or manual disimpaction. The other treatment pathway was the same except there was the addition of methylnaltrexone to oral laxatives.
The duration of the model was four months and methylnaltrexone was given every four days, based on the pattern of usage in the open-label phase of the pivotal trial.

Quality of life values were estimated from an EQ5D study conducted in the Netherlands. The model predicted that patients in the comparator sequence spend 59.48 days with symptoms and 52.52 days without symptoms. This compared to 29.63 days and 82.37 days respectively in the methylnaltrexone arm of the model. Given the better quality of life on days without constipation, this equated to a gain in QALYs of 0.01963 over the four months of assumed treatment. The methylnaltrexone arm of the model had costs of £640.64 compared to £6.90, a difference of £633.74, giving rise to a cost per QALY of £32,284. The results were also expressed as £21.23 per extra symptom-free day or £88.46 per quality adjusted life day.

It should be noted that relatively conservative estimates were included in the analysis in terms of savings associated with reduced requirements for enemas and manual disimpaction procedures associated with methylnaltrexone use. Additionally, possible benefits of allowing constipation to be managed at home rather than in an in-patient care setting were not considered. It should also be noted that the use of the QALY is not without its difficulties when dealing with palliative care situations, given the short duration over which QALYs can accumulate and the generally poor quality of life that patients may have at this stage of their illness.

Given these issues the committee concluded that methylnaltrexone could be accepted for use despite the relatively high cost-effectiveness ratio.

*Other data were also assessed but remain commercially confidential.*

**Summary of patient and public involvement**

Patient interest group submissions were received from:
- Action on Pain
- Highland Hospice
- Marie Curie Cancer Care

**Additional information: guidelines and protocols**

In 2000, the Scottish Intercollegiate Guidelines Network (SIGN) number 44. ‘Control of Pain in Cancer Patients.’ recommended that: ‘patients receiving an opioid must have access to regular prophylactic laxatives. A combination of stimulant and softening laxative will be required.’ This guideline is at present under revision; revised version expected summer 2008.

**Additional information: comparators**

In the second week of the double-blind phase of the above study, the EMEA concluded that methylnaltrexone was equivalent to the rescue medication used. Therefore the comparators used in the cost table are enemas and suppositories.
## Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per dose (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylnaltrexone</strong></td>
<td>8 to 12mg on alternate days</td>
<td>21</td>
</tr>
<tr>
<td>Docusate sodium enema</td>
<td>120mg in 10g single dose unit as required</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Fleet® Ready-to-use Enema</strong></td>
<td>118ml dose as required</td>
<td>0.46</td>
</tr>
<tr>
<td>Micralax Micro-enema®</td>
<td>5ml dose as required</td>
<td>0.41</td>
</tr>
<tr>
<td>Fletchers’ phosphate enema®</td>
<td>128ml dose as required</td>
<td>0.41</td>
</tr>
<tr>
<td>Relaxit Micro-enema®</td>
<td>5ml dose as required</td>
<td>0.32</td>
</tr>
<tr>
<td>Micolette Micro-enema®</td>
<td>5ml dose as required</td>
<td>0.31</td>
</tr>
<tr>
<td>Glycerin suppositories</td>
<td>1 to 2 4g suppositories as required</td>
<td>0.11 to 0.22</td>
</tr>
<tr>
<td>Bisacodyl suppositories</td>
<td>10mg in the morning</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do **not** imply therapeutic equivalence. Costs from eVadis on 3rd September 2008.

### Additional information: budget impact

The manufacturer estimated a gross drug budget impact of £7k in year one rising to £59k in year five. As the treatment is not replacing another therapy, there was no estimate of net drug budget impact. The manufacturer assumed that 212 patients would be eligible for treatment and that the market share would be 11% in year one rising to 90% by year five (i.e. 23 patients treated in year one, 191 by year five). The calculations assumed a duration of treatment of 2 months.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 October 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/

The undernoted reference was supplied with the submission. Those shaded grey are additional to those supplied with the submission.


