Methylnaltrexone bromide (Relistor) for opioid-induced constipation in adult patients with chronic non-malignant pain

SUMMARY

Methylnaltrexone bromide (Relistor) is administered subcutaneously (SC) and intended for use as a first or subsequent line therapy for the treatment of opioid-induced constipation in adult patients with chronic non-malignant pain. If licensed, methylnaltrexone bromide will offer an additional treatment option for such patients. Methylnaltrexone bromide is a selective peripherally acting opioid mu-receptor antagonist. As a quaternary amine it has a restricted ability to cross the blood-brain barrier, and this allows it to function as a peripherally acting mu-opioid antagonist in tissues such as the gastrointestinal tract, without impacting opioid-mediated analgesic effects on the central nervous system. Methylnaltrexone bromide (as SC formulation) is currently licenced in the EU for treatment of adult patients with opioid-induced constipation in advanced illness who are receiving palliative care when response to usual laxative therapy has not been sufficient.

The prevalence of opioid-induced constipation is not known, however, in England in 2013, there were 21,710,300 prescription opioid analgesic items dispensed. Research suggests that up to 90% of patients treated with opioids will experience chronic constipation. Constipation can contribute to secondary complications including abdominal distension, urinary retention, nausea, vomiting, anorexia, haemorrhoids, anal fissures, perianal abscesses, and intestinal obstruction which may lead to life-threatening faecal impaction additionally the debilitating symptoms of opioid-induced constipation can seriously impair patients’ quality of life.

Management of opioid-induced constipation may involve dietary and lifestyle changes in addition to medication such as bulk-forming laxatives, stimulant laxatives, osmotic laxatives or faecal softeners. When oral laxative therapy is ineffective use of suppositories, enemas, prucalopride, rectal irrigation or manual disimpaction may be appropriate. Methylnaltrexone bromide is currently in one phase III trial comparing its effect on rescue-free bowel movements against treatment with placebo.
TARGET GROUP

- Opioid-induced constipation: adult patients with chronic non-malignant (non-cancer) pain – first or subsequent line.

TECHNOLOGY

DESCRIPTION

Methylnaltrexone bromide (Relistor) is a selective peripherally acting opioid mu-receptor antagonist that has an alkyl substituent added to the nitrogen atom of the tertiary opioid antagonist\(^1\). As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted, which allows methylnaltrexone bromide to function as a peripherally acting mu-opioid antagonist in tissues such as the gastrointestinal tract, without impacting opioid-mediated analgesic effects on the central nervous system. In a phase III clinical trial methylnaltrexone bromide was administered by subcutaneous (SC) injection at 12mg every day or every other day\(^2,17\).

Methylnaltrexone bromide (as SC formulation only) is currently licenced in the EU for treatment of adult patients with opioid-induced constipation in advanced illness who are receiving palliative care when response to usual laxative therapy has not been sufficient. Very common (>10%) adverse effects (AEs) of methylnaltrexone bromide when used for its licenced indication include abdominal pain, nausea, diarrhoea, and flatulence. Common (≥1% to <10%) AEs include dizziness, hyperhidrosis, and injection site reactions (e.g. stinging, burning, pain, redness, and oedema).

An oral formulation of methylnaltrexone bromide is currently in phase III clinical trials for opioid-induced constipation in adult patients with chronic non-malignant pain.

INNOVATION and/or ADVANTAGES

If licensed, methylnaltrexone bromide will offer an additional treatment option for opioid-induced constipation in adult patients with chronic non-malignant pain.

DEVELOPER

TMC Pharma Services Ltd (EU licence holder); LINK Healthcare; Ono Pharmaceutical; Progenics Pharmaceuticals; Salix Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Methylnaltrexone bromide is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Chronic pain is defined as pain that persists beyond normal tissue healing time, which is assumed to be three months. It may arise due to numerous conditions, including back pain, osteoarthritis, fibromyalgia, and headache\(^3\). Opioids are increasingly used for the
management of chronic severe pain of non-malignant origin. Opioids have been shown to be effective in decreasing pain and improving sleep, functioning, and quality of life in patients with these conditions, but opioid use is also associated with multiple adverse effects, including constipation, which can lead to discontinuation of treatment. Additionally, research suggests that patients with opioid-induced constipation report significant increases in physician visits and sickness-related absence from work, compared with opioid users who do not experience constipation. The effects of opioids on the gut are primarily mediated by mu-opioid receptors in the gastrointestinal tract. Opioid binding to these receptors decreases enteric nerve activity and gastrointestinal propulsive motor activity, inhibits ion and fluid secretion, and increases resorption of water, leading to constipation.

The term constipation describes the subjective impression that the contents of the intestine are not evacuated at adequate frequency, in adequate volumes, the consistency of the stool is too hard, and/or the stool is passed with discomfort. Constipation can also contribute to secondary complications including abdominal distension, urinary retention, nausea, vomiting, anorexia, haemorrhoids, anal fissures, perianal abscesses, and intestinal obstruction which may lead to life-threatening faecal impaction. The debilitating symptoms of opioid-induced constipation can seriously impair patients' quality of life comparable even to pain, up to a point where some prefer inadequate pain control to avoid these side effects.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Improving quality of life for people with long term conditions (2013).

**CLINICAL NEED and BURDEN OF DISEASE**

Reported prevalence rates of constipation in the UK vary widely between studies, with figures ranging from 4% to 20%. In 2012, there were 60,567 admissions for constipation (ICD-10 K59.0) in England, resulting in 151,319 bed days and 72,567 finished consultant episodes; in the same year there were 58 deaths registered in England and Wales due to constipation. The prevalence of opioid-induced constipation is not known, however, in England in 2013, there were 21,710,300 prescription opioid analgesic items dispensed with a total net cost of £289,751,800. Research suggests that up to 90% of patients treated with opioids will experience chronic constipation and of those receiving standard laxative treatments, over half will remain dissatisfied with the outcome. The population likely to be eligible to receive methylnaltrexone bromide could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

Other Guidance

• The British Pain Society. Opioids for persistent pain: Good practice. 201012.

CURRENT TREATMENT OPTIONS

The first step in the management of constipation should be appropriate dietary and lifestyle changes13. Patients should be advised on adequate fluid intake and consuming adequate amounts of food with a high fibre content (such as fruit, vegetables, high-fibre bread, baked beans and wholegrain breakfast cereals)14. A short course of laxatives may relieve symptoms and restore normal bowel function. There are several laxatives available for this purpose, including12,15:

• Bulk-forming laxatives such as methylcellulose, ispaghula (psyllium) husk, sterculia,
• Stimulant laxatives such as bisacodyl, senna, sodium picosulfate.
• Faecal softeners such as liquid paraffin and docusate sodium.
• Osmotic laxatives such as macrogols (polyethylene glycols), lactulose, and magnesium salts (magnesium hydroxide or magnesium sulphate).

Long-term laxative use should be avoided where possible. When oral laxative therapy is ineffective at producing a bowel movement, a suppository (such as glycerol or sodium phosphate) or enema may be appropriate12,14. For women in whom treatment has failed to provide adequate relief after use of two laxatives, the prokinetic treatment prucalopride may also be used. Rectal irrigation and manual disimpaction are alternative treatment options for those who continue to have rectal emptying difficulties14.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00529087, methylnaltrexone bromide (SC) vs. placebo; phase III.</th>
</tr>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Salix Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication16, trial registry17.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and Canada.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=460; 18 years and older; opioid-induced constipation and chronic non-malignant pain; taking oral, transdermal, intravenous, or subcutaneous opioids for chronic non-malignant pain.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to methylnaltrexone bromide 12mg/day SC; methylnaltrexone bromide 12mg/every other day SC; or SC placebo daily.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for 4 weeks, then an 8 week open-label as-needed dosing phase, follow-up 2 weeks.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Percentage of patients having a rescue-free bowel movement (RFBM) within 4 hours of the first dose and percentage of active injections resulting in any RFBM within 4 hours of injection during the double-blind period.</td>
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* A rescue-free bowel movement was defined as a bowel movement where no laxatives were used during the prior 24 hours.
Secondary outcome/s

Time to first RFBM after injection, change in weekly number of RFBMs, improvements in Bristol Stool Form Scale scores, Straining Scale scores, Sense of Complete Evacuation Scale scores, use of rescue laxatives, pain intensity scores, Subjective Opiate Withdrawal Scale scores, Objective Opiate Withdrawal Scale scores, QoL measured using the Patient Assessment of Constipation–Quality of Life (PAC-QOL) questionnaire.

Key results

In the methylnaltrexone bromide daily, every other day, and placebo groups, respectively: percentage having a RFBM within 4 hours or first dose, 33.3%, 35.1%, 9.9%; percentage of active injections resulting in any RFBM within 4 hours of injection, 28.9%, 30.2%, 9.3%; adjusted mean change from baseline in weekly number of RFBMs, 3.1, 2.1, 1.5.

Adverse effects (AEs)

Very common (>10%) AEs in methylnaltrexone bromide daily group and every other day group respectively: abdominal pain 19.3%; abdominal pain 15.5%, diarrhoea 11.5%, nausea 11.5%.

ESTIMATED COST and IMPACT

COST

Methylnaltrexone bromide (SC) is already marketed in the UK for the treatment of adult patients with opioid-induced constipation in advanced illness, receiving palliative care with an insufficient response to usual laxative therapy; a 0.6mL vial (20mg/mL) costs £21.05.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other: wider societal benefits - earlier return to normal activities, including employment.
- Reduced symptoms or disability
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services: reduced complications of opioid therapy.
- Re-organisation of existing services
- Need for new services
- Other:
  - None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs: reduced complications of opioid therapy.
- Other:
  - None identified

Other Issues

- Clinical uncertainty or other research question identified
  - None identified