

Methylnaltrexone injections (Relistor) for opioid-induced constipation in palliative care

(METH-il-nal-TREX-own)

Summary

- Methylnaltrexone is an option for treating opioid-induced constipation in people receiving palliative care who have not responded to adequately titrated laxatives.
- Methylnaltrexone increases bowel movements without reversing analgesia.
- Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.
- Exclude bowel obstruction before using methylnaltrexone.
- Around 50–60% of people with opioid-induced constipation experience a bowel movement within 4 hours of a single dose of methylnaltrexone. However, around 30% of people may not respond within 24 hours of a single dose.
- The recommended dose varies with weight.
- Only use methylnaltrexone in addition to other therapies that prevent or treat opioid-induced constipation.
- Ensure that toileting facilities are accessible, as bowel movements may occur within 30 minutes of an injection.
- Do not use methylnaltrexone more than once every 24 hours.
- Mild to moderate gastrointestinal adverse effects are common.

PBS listing

Authority required

Methylnaltrexone is listed on the palliative care schedule for treatment, in combination with oral laxatives, of opioid-induced constipation that has failed to respond to laxatives.

Initial supply is for 3 doses. If the patient responds, a further 7 doses with up to 3 repeats may be prescribed. Subsequent and continuing supply of a further 7 doses with up to 3 repeats requires a response to methylnaltrexone **and** consultation with a palliative care specialist or service. However, if a palliative care specialist or service is not consulted, supply is limited to a further 7 doses with no repeats for people who have responded to methylnaltrexone.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended methylnaltrexone for listing on the basis of high clinical need. Methylnaltrexone was considered to have acceptable cost-effectiveness compared with placebo.¹

Place in therapy

Methylnaltrexone is an opioid antagonist that, in clinical doses, is unable to cross the blood–brain barrier. Therefore, it can reverse the effect of opioids in the peripheral nervous system and relieve constipation without reversing the analgesic effect of opioids in the central nervous system (CNS).

Methylnaltrexone is only registered for use in palliative care patients with opioid-induced constipation. It is administered as a subcutaneous injection. It may be an option for people who have opioid-induced constipation that has not responded to adequately titrated laxatives, and in whom bowel obstruction has been excluded. Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.

Methylnaltrexone is a quaternary amine derivative of naltrexone

Opioid analgesia is the result of agonist actions on opioid receptors in the CNS.^{2,3} However, constipation is primarily the result of opioid actions on receptors in the bowel.³

Naltrexone is an opioid antagonist that can cross the blood–brain barrier. It may reverse opioid-induced constipation but will also reverse the analgesic effect of opioids in the CNS.^{2,4,5}

Methylnaltrexone is produced by adding a methyl group to naltrexone.⁵ This increases the polarity and lowers the lipid solubility of the molecule, preventing it from crossing the blood–brain barrier when it is given in clinically appropriate doses.^{4,5} As a result, methylnaltrexone does not reverse opioid analgesia.

Methylnaltrexone increases bowel movements in opioid-induced constipation

In placebo-controlled trials, around 50–60% of people in palliative care with opioid-induced constipation defecated within 4 hours of the first dose of methylnaltrexone (Table 1). Around 30% of people did not respond to a single dose of methylnaltrexone after 24 hours.⁶

Table 1: Proportion of trial participants who defecated within 4 hours of the first dose of methylnaltrexone or placebo

	n	% responders		
		Methylnaltrexone 0.15 mg/kg	Methylnaltrexone 0.30 mg/kg	Placebo
Slatkin et al. ⁶	154	62%	58%	14%
Thomas et al. ⁷	133	48%	—	15%

Almost all trial participants were using laxatives at baseline but had not defecated for more than 48 hours or had had fewer than 3 bowel movements in the previous week, with no clinically significant defecation in the previous 24 hours.^{6,7} Participants were using a median of 2 classes of laxatives but it is unclear if this was optimal laxative therapy. Adjusting the laxative regimen may have resulted in adequate defecation without the need for methylnaltrexone.

Just over 200 people in these two trials received methylnaltrexone on an 'as needed' basis for up to 4 months during open-label extensions of the trials. While more than half of the people who entered the open-label studies withdrew or died — usually because of underlying disease progression — the overall response rate was similar to that achieved during the randomised trials: around 50–60% of participants defecated within 4 hours of receiving methylnaltrexone.^{6,7}

Up to 50% of people may not respond to a particular instance of receiving methylnaltrexone. However, in one trial in which participants received 7 doses of methylnaltrexone or placebo over a 2-week period the response rates were 79% and 46%, respectively.⁷

Methylnaltrexone does not reverse analgesia

Mean pain scores and opioid withdrawal scores among trial participants receiving methylnaltrexone did not change from baseline. No difference in mean pain or opioid withdrawal scores was reported in the methylnaltrexone or placebo groups.^{6,7}

Patients may choose to use lower doses of opioids than necessary for complete analgesia because of unacceptable constipation. It is not known whether the use of methylnaltrexone would allow the opioid dose to be increased in such patients, as no study provided this information.

Continue other therapies to prevent or treat opioid-induced constipation

Trial participants using laxatives at baseline continued to use them throughout the trials of methylnaltrexone.^{6–8}

Laxatives should be routinely prescribed whenever opioids are used.^{9,10} Consider a combined stimulant laxative with stool softener (eg, Coloxyl with Senna).^{2,9} Titrate the dose every few days until comfortable defecation is achieved and increase laxative doses if the opioid dose increases.¹¹

Continue non-drug interventions to prevent or treat opioid-induced constipation. These include ensuring adequate fluid intake, encouraging mobility if possible and encouraging bowel movements at the same time each day.^{2,9} Avoid bulking agents and high-fibre diets in people receiving palliative care.^{2,9}

No studies have compared the efficacy of methylnaltrexone with other pharmacological or non-pharmacological treatments of constipation. No study has investigated whether methylnaltrexone can prevent opioid-induced constipation.

Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.

Safety issues

Common adverse effects include abdominal pain, flatulence, nausea and dizziness.^{6–8,12} Because of the small number of palliative care patients (n = 320) enrolled in trials of methylnaltrexone, information on the full adverse-effect profile remains limited. No trial has lasted longer than 4 months.^{6–8,12}

Bowel obstruction should be ruled out before using methylnaltrexone.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Adverse effects were common but usually mild to moderate

In trials undertaken in palliative care patients, abdominal pain, flatulence, nausea and dizziness were reported more frequently in people taking methylnaltrexone than placebo (Table 2).^{6–8,12} Symptoms were generally reported to be mild or moderate.

Table 2: Commonly increased adverse effects in trials of methylnaltrexone against placebo^{6,7}

Adverse effect	Methylnaltrexone*	Placebo
Abdominal pain	17–38%	4–13%
Flatulence	13–15%	4–7%
Nausea	4–15%	2–7%
Dizziness	4–9%	0–3%

* Methylnaltrexone doses of 0.15 mg/kg or 0.3 mg/kg

There has been 1 death considered to be partly related to the use of methylnaltrexone. A 73-year-old woman with metastatic breast cancer developed severe diarrhoea, nausea, vomiting and syncope after 3 doses of 0.3 mg/kg methylnaltrexone within a few days. Supportive intervention was limited to comfort measures but rehydration was not attempted. The cause of death was listed as metastatic breast cancer, exacerbated by diarrhoea, subsequent dehydration and cardiovascular collapse.⁶

Dosing Issues

Methylnaltrexone is administered as a subcutaneous injection into the upper arm, thigh or abdomen.¹² Each dose is supplied in a single-use vial containing 12 mg methylnaltrexone in 0.6 mL water. Single-use syringes are also provided in the 7-dose packs.[†] The recommended dose varies with weight (Table 3).

Table 3: Recommended dose of methylnaltrexone¹²

Patient weight	Dose	Injection volume
< 38 kg	0.15 mg/kg	Weight (kg) × 0.0075; rounded to nearest 0.1 mL
38–61 kg	8 mg	0.4 mL
62–114 kg	12 mg	0.6 mL
> 114 kg	0.15 mg/kg	Weight (kg) × 0.0075; rounded to nearest 0.1 mL

Inject methylnaltrexone as needed but do not use more than once every 24 hours.

Typically, methylnaltrexone is administered every second day but it is possible to wait longer between injections if such frequent dosing is unnecessary.¹² Alternatively, if there has been no bowel movement within 24 hours of an injection, another dose may be administered.¹² However, do not use methylnaltrexone more than once every 24 hours.¹²

Methylnaltrexone can be administered by the patient or a carer. Instructions on preparing and administering a dose of methylnaltrexone are included with each vial or pack of methylnaltrexone. Vials should only be used once: ensure patients and carers understand how to

[†] Methylnaltrexone is available in a single or 7-dose pack.

dispose of unused liquid and needles safely. Patient information booklets will be distributed to prescribing doctors and are also available from the sponsor.

Ensure toileting facilities are accessible, as bowel movements may occur within 30 minutes of an injection.^{6,7,12}

Information for patients

- Use methylnaltrexone as needed but do not use more than once every 24 hours.
- Common adverse effects include mild to moderate abdominal pain, nausea and flatulence.

- Use a different site for each injection and do not inject into areas where the skin is tender, bruised, red or hard.¹²
- You may have a bowel movement as soon as 30 minutes after an injection. Ensure that toileting facilities are easily accessible.
- Vials should only be used once: discard unused liquid and needles safely.¹²
- Half of all people who have responded to a dose of methylnaltrexone do so within 4 hours.

Discuss the Relistor (methylnaltrexone) consumer medicine information (CMI) leaflet with the patient.

References

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