Abstract

Methylnaltrexone is a selective μ-opioid receptor antagonist that has restricted ability to cross the blood-brain barrier, thus enabling reversal of opioid-induced peripheral effects, such as constipation, without affecting the central effects, such as pain relief.

Treatment with subcutaneous methylnaltrexone 0.15–0.30 mg/kg, relative to placebo, significantly increased the rescue-free laxation response rate within 4 hours of the first dose (primary endpoint) in adult patients with opioid-induced constipation and advanced illness in two randomized, double-blind, placebo-controlled, multicentre, phase III studies; one was a single-dose study (n = 154), the other a multiple-dose study (n = 133).

In the multiple-dose study, rescue-free laxation response rates within 4 hours after at least two of the first four doses (coprimary endpoint) were also significantly higher in methylnaltrexone recipients than in placebo recipients.

Moreover, median time to laxation after the first dose was significantly shorter in methylnaltrexone recipients than in placebo recipients in both studies.

Methylnaltrexone was not associated with any significant changes in pain scores or central opioid withdrawal in these studies.

Methylnaltrexone was generally well tolerated in clinical trials; most adverse events were of mild to moderate severity.
Opioid analgesics, while used extensively for moderate to severe pain management, are frequently associated with adverse events.[1,2] Opioids act on the same receptor classes (μ-, δ- and κ-opioid receptors) regardless of whether the end result is pain relief or an adverse event, making it difficult to provide pain relief without the associated adverse events.[2] One of the most common adverse events is constipation, occurring in >85% of cancer[3,4] and >40% of non-cancer[5] patients treated with opioids. As well as being uncomfortable, constipation can lead to complications such as abdominal distension, vomiting, and gut obstruction and perforation.[6]

Constipation is a well-known opioid-associated adverse event; guidelines recommend prophylactic treatment with laxatives (such as bisacodyl,[7,8] polyethylene glycol[8] or lactulose[8]), and subsequent or additional treatment with other laxatives if constipation persists.[7,8] However, constipation may continue despite these standard treatments; in these circumstances, treatment with methylnaltrexone bromide (methylnaltrexone; Relistor®) is a recommended option.[8] As a quaternary amine, methylnaltrexone has restricted ability to cross the blood-brain barrier.[9] Therefore, the effects of methylnaltrexone are greater in peripheral tissues, such as the gastrointestinal tract, where it acts to relieve opioid-induced constipation, than in the CNS, where opioid-induced analgesia is not markedly affected.[8,9]

This article provides an overview of the pharmacological properties of subcutaneous methylnaltrexone and reviews the clinical trial data available on the efficacy and tolerability of the drug in the treatment of opioid-induced constipation in patients with advanced illness. Medicinal literature on the use of methylnaltrexone in the approved indication was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Pharmacodynamic data for methylnaltrexone are available from several fully published in vitro,[10-13] animal[14-17] and human[18-25] studies, supplemented by data from the US prescribing information[9] and the EU summary of product characteristics (SPC).[26]

- Methylnaltrexone is a selective μ-opioid receptor antagonist.[10] In vitro studies have demonstrated that methylnaltrexone reverses the effects of μ- and, to a lesser extent, κ-, but not δ-opioid agonists,[10] and has a much lower receptor binding affinity than naltrexone.[11] The concentration of methylnaltrexone required to reverse the effects of κ-opioid agonists was ≈19-fold higher than that required to reverse the effects of μ-opioid agonists.[10] The concentration of methylnaltrexone required to displace 50% of stereospecifically bound [3H]etorphine from opiate receptors was 42- and 77-fold (in the absence and presence, respectively, of sodium chloride) higher than that of naltrexone.[11] Additionally, the concentration of methylnaltrexone required to produce 50% of maximum contraction in ilea isolated from morphine-treated guinea pigs was 26-fold higher than that of naltrexone.[11]

- Further in vitro studies showed that methylnaltrexone increased gut motility in equine tissue[12] and decreased morphine-induced inhibition of contraction of the guinea-pig ileum[13] and the human intestine.[13] Furthermore, in rats, methylnaltrexone dose-dependently decreased opioid-induced gastrointestinal transit time delay.[9]

- When administered subcutaneously,[18] orally[19] or intravenously,[20-23] methylnaltrexone decreased opioid-induced delays in oral-caecal transit time[18,19,21-23] and gastric emptying[20] in a non-randomized, single-blind pilot study in chronic methadone users[23] and several randomized, double-blind, placebo-controlled studies in healthy
volunteers or chronic methadone users. For example, in six healthy adult volunteers, the oral-caecal transit time increased from 85 minutes at baseline to 110 minutes following intravenous morphine plus subcutaneous methylnaltrexone 0.1 mg/kg, compared with 155 minutes following intravenous morphine plus placebo (statistical data not reported). Similarly, when intravenous morphine was coadministered with subcutaneous methylnaltrexone 0.3 mg/kg, oral-caecal transit times increased from 98 minutes at baseline to 108 minutes, compared with 140 minutes following morphine plus placebo (p < 0.05).

- As a quaternary amine, methylnaltrexone has a restricted ability to cross the blood-brain barrier. This was demonstrated in several animal studies in which parenterally administered methylnaltrexone was associated with decreased opioid-induced peripheral effects and/or generally no significant changes in opioid-induced central effects. In one study, morphine-induced analgesia was not significantly reduced in rats pre-treated with methylnaltrexone 1–60 mg/kg for 10 minutes or 1–16 mg/kg for 50 minutes prior to morphine administration. However, morphine-induced analgesia was significantly (p < 0.01) reversed when methylnaltrexone was administered 50 minutes (dose of 30 mg/kg) and 80 minutes (8 mg/kg) before morphine administration. These significant changes in a central effect were attributed to the potential demethylation of methylnaltrexone to naltrexone (a tertiary amine that readily crosses the blood-brain barrier). Another study also showed some significant changes in central effects at high doses in mice.

- Additionally, following the administration of remifentanil (a specific μ-opioid receptor agonist that acts in the CNS to cause pupillary constriction) in humans, the administration of naloxone but not methylnaltrexone or placebo was associated with a change in pupillary constriction.

- Clinical evidence supports these data, suggesting that methylnaltrexone has a restricted ability to cross the blood-brain barrier. In two randomized, double-blind, placebo-controlled, multicentre studies in patients with opioid-induced constipation and advanced illness (see section 3), there was no significant change from baseline in pain scores (rated from 0 [no pain] to 10 [worst pain imaginable]) following administration of subcutaneous methylnaltrexone 0.15 or 0.30 mg/kg (as a single dose), methylnaltrexone 0.15–0.30 mg/kg (multiple doses) or placebo.

- Moreover, central opioid withdrawal did not occur with subcutaneous administration of methylnaltrexone in these studies. For example, in the single-dose study, mean changes in scores on the modified Himmelsbach opioid withdrawal scale (scores range from 7 to 28; higher score means greater severity of withdrawal symptoms) from baseline to 4 hours post dose were −0.21 (from 8.11), −0.17 (from 7.91) and −0.16 (from 7.71) in methylnaltrexone 0.15 and 0.30 mg/kg and placebo recipients, respectively.

- Several preclinical (in vitro and animal) studies have shown that methylnaltrexone administered with anticancer drugs (including rapamycin inhibitors, 5-fluorouracil and bevacizumab) may exert a synergistic antiproliferative and antiangiogenic effect.

- Animal studies have also demonstrated a potential antiobesity effect with methylnaltrexone, with decreases in bodyweight and fat observed in mice and rats.

- Methylnaltrexone had no significant effect on the corrected QT interval in a randomized, double-blind, crossover study in which 56 healthy volunteers received intravenous methylnaltrexone 0.30 and 0.64 mg/kg, open-label oral moxifloxacin (positive control) and placebo, and in a randomized, double-blind, parallel-group study in which 207 healthy volunteers received single-dose methylnaltrexone 0.15, 0.30 or 0.50 mg/kg, moxifloxacin (positive control) or placebo.

### 2. Pharmacokinetic Profile

Pharmacokinetic data for subcutaneous methylnaltrexone are taken from the US prescribing information and the EU SPC; most data are from an unspecified population.

- Subcutaneous methylnaltrexone is rapidly absorbed, with a median time to maximum plasma concentration (Cmax) of ~0.5 hours. Following single doses of methylnaltrexone 0.15 or 0.30 mg/kg, mean Cmax values were 117 or
239 ng/mL and mean area under the plasma concentration-time curve (AUC) from time zero to 24 hours (AUC_{24}) values were 175 or 362 ng mL\(^{-1}\) h mL\(^{-1}\). Equilibrium dialysis determined that 11.0–15.3\% of methylaltrexone is bound to human plasma proteins. The volume of distribution of methylaltrexone at steady state is \(\approx 1\) L kg\(^{-1}\), indicating moderate tissue distribution. Following administration of radioactive methylaltrexone in a mass-balance study, \(\approx 60\%\) of administered radioactivity was recovered with five distinct metabolites. Methylaltrexone appears to be metabolized primarily by conversion to methyl-6-naltrexol isomers (5\% of the administered radioactivity) and methylaltrexone sulfate (1.3\%). No significant N-demethylation of methylaltrexone to naltrexone was observed. Most (85\%) of the administered radioactive methylaltrexone was eliminated as unchanged drug; \(\approx 50\%\) was excreted in the urine and less in the faeces. Methylaltrexone has a terminal elimination half-life of \(\approx 8\) hours.

Patients with severe renal impairment (creatinine clearance \(< 30\) mL/min [1.8 L/h]) who received a single dose of methylaltrexone 0.30 mg/kg had an 8- to 9-fold decrease in renal clearance and a 2-fold increase in total exposure, but no change in \(C_{\text{max}}\) values. There was no clinically significant effect of mild or moderate hepatic impairment on methylaltrexone AUC or \(C_{\text{max}}\) values. A dose reduction is recommended in patients with severe renal impairment (section 5), but not in those with mild or moderate renal or hepatic impairment. The pharmacokinetics of methylaltrexone have not been investigated in patients with end-stage renal impairment or severe hepatic impairment. Pharmacokinetic data from healthy volunteers have shown that methylaltrexone dose-adjusted exposure increases as patient bodyweight increases. In vitro drug metabolism studies have shown that methylaltrexone is a weak inhibitor of cytochrome P450 (CYP) 2D6, but does not significantly inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19 or CYP3A4. However, a clinical drug interaction study in healthy adult male volunteers showed that subcutaneous methylaltrexone 0.30 mg/kg did not have a significant effect on dextromethorphan (a CYP2D6 substrate) metabolism. No studies investigating drug interactions between methylaltrexone and drugs that are actively renally excreted have been carried out in humans. In addition, no clinically significant change in methylaltrexone AUC or \(C_{\text{max}}\) was found before or after administration of multiple doses of cimetidine in 18 healthy volunteers.

### 3. Therapeutic Efficacy

The efficacy of subcutaneous methylaltrexone for the treatment of opioid-induced constipation in patients with advanced illness has been investigated in a 1-week, randomized, double-blind, multicentre, dose-ranging study and two randomized, double-blind, placebo-controlled, multicentre, phase III studies (MNTX 301 and MNTX 302). All data are fully published. Discussion here focuses on the two phase III trials.

MNTX 301 comprised of an initial double-blind phase, during which patients received a single dose of methylaltrexone 0.15 or 0.30 mg/kg or placebo. After completing this phase, patients could enrol in a 4-week, open-label phase, during which they received methylaltrexone as required up to once every 24 hours (initial dose was 0.15 mg/kg; range 0.075–0.3 mg/kg) \(n = 136\). MNTX 302 comprised a 2-week double-blind phase in which patients received methylaltrexone 0.15 or 0.30 mg/kg (based on clinical response) or placebo on alternate days.

Both studies included 3-month, open-label extension periods after the open-label (27 patients entered the extension; 9 completed) or double-blind (89 patients entered the extension, 82 received at least one methylaltrexone dose; the number of patients who completed the phase was not reported) phases, during which patients received methylaltrexone as required up...
to once every 24 hours (initial dose was the same as the last dose received during the first open-label phase\cite{24} or 0.15 mg/kg,\cite{25} range 0.075–0.3 mg/kg\cite{24,25} [\cite{24,25}].

Eligible patients were aged ≥18 years and had advanced illness (defined as a terminal disease\cite{25}) with a life expectancy of ≥1\cite{25} or 1–6 months.\cite{24} Patients were also required to have been receiving opioids for analgesia for ≥2 weeks,\cite{25} to have been on a stable regimen of opioids and laxatives for ≥3 days before study entry,\cite{24,25} and to have opioid-induced constipation (<3 laxations during preceding week plus no clinically meaningful laxation within 24 hours before the first dose\cite{25} or no clinically meaningful laxation within 48 hours before the first dose\cite{24,25}).

Exclusion criteria included constipation not caused by opioids,\cite{24,25} mechanical gastrointestinal obstruction,\cite{24,25} a peritoneal catheter,\cite{24,25} clinically significant active diverticular disease,\cite{24,25} faecal impaction,\cite{24,25} surgically acute abdomen\cite{24,25} and faecal ostomy.\cite{24,25}

The primary outcome was the rescue-free laxation response rate within 4 hours of the single-\cite{24} first\cite{25} dose, with a coprimary endpoint in one study of the rescue-free laxation response rate within 4 hours of at least two of the first four doses.\cite{25} Assessments were conducted using the modified intent-to-treat population in both phase III studies (patient numbers reported in this section are from this population unless otherwise specified)\cite{24,25} with last-observation-carried-forward imputation for missing values in MNTX 302.\cite{25} Secondary efficacy outcomes included the rescue-free laxation response rate within 24 hours of each dose,\cite{24,25} time to (rescue-free) laxation,\cite{24,25} stool consistency (rated from 1 [very hard] to 6 [watery]),\cite{24,25} constipation distress (rated from 1 [none] to 5 [very much]),\cite{24,25} the Global Clinical Impressions of Change scale (GCIC; rated from 1 [much worse] to 7 [much better]; improvement defined as a score of 5–7)\cite{24,25} and the rescue-free laxation response rate within 4 hours of at least four of all seven doses (in the multiple-dose study).\cite{25}

At baseline, the median age was 66\cite{24} or =71\cite{25} years, with a range of 21–100\cite{24} and 34–98 years, respectively.\cite{25} Approximately half the patients were male and most patients in both studies were Caucasian (>80%).\cite{24,25} Primary diagnoses included cancer (81\%\cite{24} and 58\%\cite{25}) and cardiovascular disease (5\%\cite{24} and 11\%\cite{25}). More than half the patients in each study had a WHO performance status of 3 or 4 (67\%\cite{24} and 71\%\cite{25}) and constipation distress ratings of ‘quite a bit’ or ‘very much’ (56\%\cite{24} and 62\%\cite{25}).

Patients in both studies took a mean of two different classes of laxative. The most common laxatives used were contact (stimulant) laxatives (83\%\cite{24} and 81\%\cite{25}), osmotic laxatives (56\%\cite{24} and 32\%\cite{25}) and stool softeners (27\%\cite{24} and 40\%\cite{25}). Median opioid dosages (oral morphine equivalents) at study entry were 186.5 mg/day in the single-dose study;\cite{24} in the multiple-dose study, median dosages were 100 mg/day in the placebo group and 150 mg/day in the methylnaltrexone group.\cite{25} In the multiple-dose study, 20 of 62 (32\%) methylnaltrexone and 21 of 71 (30\%) placebo recipients received a dose escalation during the second week.\cite{25}

\begin{itemize}
  \item In the dose-ranging study (n = 33), methylnaltrexone doses ≥5 mg were significantly more effective than 1 mg doses with regard to laxation within 4 hours after the initial dose (primary endpoint; 11 of 23 patients vs 1 of 10 patients; \(p = 0.05\)), and no dose-response relationship was observed with dosages above 5 mg/day.\cite{32} Separated into dose groups, three of seven methylnaltrexone 5 mg, six of ten methylnaltrexone 12.5 mg and two of six methylnaltrexone 20 mg recipients had a laxation within 4 hours after the initial dose.\cite{32}
  \item Metylnaltrexone significantly increased the rescue-free laxation response rate within 4 hours of the first dose\cite{24,25} and after at least two of the first four doses\cite{25} (primary endpoints; table I) in the phase III studies. These differences remained significant when adjustments were made for baseline opioid dose.\cite{24,25}
  \item Furthermore, in the multiple-dose study, additional post hoc, subgroup analyses demonstrated that the rescue-free laxation response rate within 4 hours after the first dose did not vary with regard to patient age, functional status or whether or not the primary diagnosis was cancer.\cite{25}
\end{itemize}
During the first 13 days in the multiple-dose study, methylnaltrexone was associated with a higher rescue-free laxation response rate than placebo within 4 hours after each dose (range 37–48% vs 7–15%; p < 0.005 at all timepoints).[23,25] A total of 39% of methylnaltrexone recipients and 6% of placebo recipients had a rescue-free laxation response within 4 hours after at least four of seven doses (p < 0.001).[24] and 79% versus 46% of patients had a rescue-free laxation response within 4 hours after at least one dose.[25] Post hoc analyses showed that methylnaltrexone recipients who had responded to all previous doses had response rates of 57–100% for the subsequent methylnaltrexone dose (i.e. doses two to seven).[33]

Methylnaltrexone recipients had a significantly shorter median time to laxation after the first dose than placebo recipients (table I).[24,25] Methylnaltrexone recipients also demonstrated a faster response than placebo recipients following all other doses in the multiple-dose study (all p < 0.002).[25] Of methylnaltrexone recipients who responded within 4 hours after the dose, approximately half showed a response within 30 minutes in both studies.[24,25]

A significantly higher rescue-free laxation response rate within 24 hours was observed in methylnaltrexone than in placebo recipients (table I).[24,25]

Among patients in the multiple-dose study who required a dose escalation in the second week, the rescue-free laxation response rate within 4 hours (as a percentage of doses) was 15% after the 0.15 mg/kg dose and 24% after the 0.30 mg/kg dose among methylnaltrexone recipients; the rates in corresponding placebo recipients were 8% and 7%.[25]

Of the patients who demonstrated a rescue-free laxation response within 4 hours in the single-dose study, watery bowel movements occurred in 28% (8 of 29) of methylnaltrexone 0.15 mg/kg and 38% (12 of 32) of methylnaltrexone 0.30 mg/kg recipients; none of the responders to placebo had watery bowel movements.[24] In the multiple-dose study, 16% (28 of 176) of methylnaltrexone and 17% (8 of 48) of placebo doses that were linked to rescue-free laxation were also associated with watery bowel movements.[25]

A total of 64% of methylnaltrexone 0.15 mg/kg, 64% of methylnaltrexone 0.30 mg/kg and 34% of placebo recipients in the single-dose study reported an improvement in constipation distress after 4 hours (statistical data not reported).[24] In post hoc analyses of the multiple-dose study, 64% of methylnaltrexone and 52% of placebo recipients reported improved constipation distress on day 7; corresponding proportions for day 14 were 60% and 54% (statistical data not reported).[33]

**Table I.** Efficacy of methylnaltrexone (MET) in adult patients (pts) with opioid-induced constipation and advanced illness. Results from two randomized, double-blind, placebo (PL)-controlled, multicentre, phase III trials.[24,25] one investigated a single dose,[24] the other a dose administered every second d for 2 wk.[25]

| Study name | Treatment (mg/kg) | No. of pts (mITT) | Response* rate within 4 h (% pts) | Response* rate within 24 h** | Median time to laxation after first dose (h) |
|------------|------------------|------------------|----------------------------------|-----------------------------|---------------------------------------------|
|            |                  |                  | after first/single dose           | after at least two of the    |                                             |
|            |                  |                  |                                 | first four doses             |                                             |
| MNTX 301[24] | MET 0.15         | 47               | 61.7**c                         | 68.1**                      | 1.1**                                       |
| (single dose) | MET 0.30         | 55               | 58.2**c                         | 63.6**                      | 0.8**                                       |
|            | PL               | 52               | 13.5c                           | 26.9                        | >24                                         |
| MNTX 302[25] | MET 0.15–0.30d   | 62               | 48**c                           | 52**c                       | 55–66*                                      |
| (multiple dose) | PL              | 71               | 15c                            | 8c                          | 29–39                                       |

a Response was defined as rescue-free laxation.

b After the single dose[24] or as a range over all seven doses.[25]

c Primary[24] or coprimary[25] endpoint.

d Pts received 0.15 mg/kg q2d in wk 1, increased to 0.30 mg/kg q2d in wk 2 if, by d 8, pts had had <3 rescue-free laxations.

mITT = modified intent-to-treat population; q2d = every 2 days; * p < 0.001, ** p < 0.0001 vs PL; † p < 0.05 vs PL for doses one to four.
• In the single-dose study, 59% of methylaltrexone 0.15 mg/kg, 59% of methylaltrexone 0.30 mg/kg and 22% of placebo recipients reported improvement in GCIC score (statistical data not reported). In the multiple-dose study, 69% of methylaltrexone and 35% of placebo recipients had an improvement in the clinician-rated GCIC score on day 7; corresponding proportions for day 14 were 68% and 50% (statistical data not reported).

• In patients receiving methylaltrexone during the 4-week open-label phase of the single-dose study, laxation response rates were generally similar between patients who had received methylaltrexone and those who had received placebo during the double-blind phase of the study. The laxation response rates within 4 hours after the initial dose were 54% in previous placebo recipients, 62% in previous methylaltrexone 0.15 mg/kg recipients and 52% in previous methylaltrexone 0.3 mg/kg recipients. Laxation response rates were also maintained over the course of the extension period of this study (numerical data not reported).

• In recipients of methylaltrexone in the extension period of the multiple-dose study, response rates (number of doses which were associated with a response divided by the total number of doses) were also generally similar between patients who had received methylaltrexone and those who had received placebo during the double-blind phase of the study. During the double-blind phase, response rates (using the above definition) were 45% for methylaltrexone and 11% for placebo recipients; in months 1–3 of the extension period, patients previously receiving methylaltrexone had response rates of 45–58% and those previously receiving placebo had response rates of 48–52%.

4. Tolerability

Tolerability data for methylaltrexone when used to treat opioid-induced constipation in patients with advanced illness are available from the two phase III trials discussed in section 3 and their open-label extension phases, supplemented by data from the US prescribing information. Adverse event severity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Methylaltrexone was generally well tolerated in patients with opioid-induced constipation and advanced illness.

• The most common adverse events in the multiple-dose trial during the double-blind phase are shown in figure 1; most of these were reportedly mild to moderate in severity. A total of 81% of methylaltrexone (n = 63) and 80% of placebo (n = 71) recipients reported any adverse event, and 6% and 7% discontinued treatment as a result of adverse events. Patients who had increased methylaltrexone dosages did not demonstrate a clinically relevant difference in the pattern of adverse events from those whose dosage stayed the same.

• The overall adverse event profile in the single-dose trial was generally similar to that observed in the multiple-dose trial. The proportions of patients with any adverse event following the double-blind dose were 72% and 80% in the methylaltrexone 0.15 (n = 47) and 0.30 (n = 55) mg/kg groups and 48% in the placebo (n = 52) group; the most common adverse event in the three groups was abdominal pain of mild to moderate severity, occurring in 28%, 38% and 4% of patients, respectively. Abdominal pain and other adverse events, including flatulence (13% and 15% of methylaltrexone 0.15 and 0.30 mg/kg recipients and 4% of placebo recipients), nausea (4%, 15% and 2%) and dizziness (4%, 9% and 0%) appeared to occur in a dose dependent manner.

• In a pooled analysis of data from the two double-blind, placebo-controlled trials of methylaltrexone 0.075, 0.15 and 0.30 mg/kg, the most common (>10% all methylaltrexone recipients) adverse events were abdominal pain (28.5% of methylaltrexone recipients vs 9.8% of placebo recipients), flatulence (13.3% vs 5.7%) and nausea (11.5% vs 4.9%).

• Longer-term methylaltrexone treatment also appeared to be generally well tolerated. The most common adverse events in the extension phase of the multiple-dose study (n = 82) were abdominal pain (30% of patients), malignant-neoplasm
progression (24%), nausea (21%) and vomiting (20%).[25]

- Severe (grade 3) adverse events in the double-blind period of the multiple-dose trial occurred in 8% of methylnaltrexone and 13% of placebo recipients, and life-threatening (grade 4) adverse events (all judged to be related to the primary illness) occurred in 16% and 15% of patients, respectively.[25] In the single-dose trial, severe adverse events occurred in 19 methylnaltrexone recipients during the double-blind and open-label periods, including abdominal pain (15 incidents), increased sweating (3 incidents) and increased pain (2 incidents).[24]

- Serious adverse events (18% of methylnaltrexone and 28% of placebo recipients) and deaths (16% and 23%) in the double-blind phase of the multiple-dose study were deemed either not related or unlikely to be related to treatment.[25] A total of 44% of patients in the open-label extension phase of this trial reported serious adverse events. In this phase, one patient had serious muscle spasms and another had serious abdominal pain and exacerbated pain; these were the only serious adverse events deemed related to study drug.[25] A total of 32 (of 82) patients died in the extension phase; all deaths were deemed consistent with underlying disease progression.

- In the single-dose study, three patients reported serious adverse events deemed related to methylnaltrexone treatment, all occurring during the open-label phase.[24] These were flushing, delirium and diarrhoea; the patient with diarrhoea died, with the cause of death determined to be metastatic breast cancer exacerbated by diarrhoea with subsequent dehydration and cardiovascular collapse.[24] All other serious adverse events (number not reported) and deaths (n = 87) were deemed unrelated to the study drug.

5. Dosage and Administration

Subcutaneous methylnaltrexone should usually be administered once every second day, but can be administered up to once every 24 hours, 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.[9,26] It should be injected in the upper arm, abdomen or thigh.[9,26] The recommended dose varies with weight. Patients weighing 84 to <136 pounds (38 to
<62 kg) should receive methylnaltrexone 8 mg in a 0.4 mL injection volume, patients weighing 136–251 pounds (62–114 kg) should receive methylnaltrexone 12 mg in a 0.6 mL injection volume, and patients weighing <84 pounds (<38 kg) or >251 pounds (>114 kg) should receive methylnaltrexone 0.15 mg/kg in an injection volume calculated by multiplying the patient weight in pounds by 0.0034 or in kilograms by 0.0075 and rounding up to the nearest 0.1 mL. [9,26]

Known or suspected mechanical gastrointestinal obstruction is a contraindication for methylnaltrexone. [9,26] The US prescribing information recommends that patients with severe renal impairment (creatinine clearance <30 mL/min [1.8 L/h]) have their methylnaltrexone dose reduced by half; [9] the EU SPC recommends these patients receive 8 mg in 0.4 mL solution if they weigh 62–114 kg or 0.075 mg/kg for those with a body-weight outside this range. [26] Therapy should be discontinued if severe or persistent diarrhoea occurs. [9]

The use of methylnaltrexone beyond 4 months has not been studied. [9,26] Local prescribing information should be consulted for contraindications, precautions and warnings, drug interactions, dosage modifications and patient monitoring requirements.

### 6. Methylnaltrexone: Current Status

Methylnaltrexone is approved in several countries, including the US [9] and EU, [26] 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. Clinical trials in adult patients have shown that methylnaltrexone is effective and generally well tolerated when used for this indication.

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