ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg/0.6 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 0.6 mL contains 12 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear solution, colourless to pale-yellow, essentially free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relistor is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.

4.2 Posology and method of administration

Posology

Opioid-induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)
The recommended dose of methylnaltrexone bromide is 12 mg (0.6 mL of solution) subcutaneously, as needed, given as at least 4 doses weekly, up to once daily (7 doses weekly).

In these patients, the treatment with usual laxatives should be stopped when commencing treatment with Relistor (see section 5.1).

Opioid-induced constipation in adult patients with advanced illness (palliative care patients)
The recommended dose of methylnaltrexone bromide is 8 mg (0.4 mL of solution) (for patients weighing 38-61 kg) or 12 mg (0.6 mL of solution) (for patients weighing 62-114 kg).

The usual administration schedule is one single dose every other day. Doses may also 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.

Patients whose weight falls outside of the ranges should be dosed at 0.15 mg/kg. The injection volume for these patients should be calculated as follows:

Dose (mL) = patient weight (kg) x 0.0075

In palliative care patients, Relistor is added to usual laxative treatment (see section 5.1).

Special populations

Elderly population
No dose adjustment is recommended based on age (see section 5.2).

Patients with renal impairment
In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the dose of methylnaltrexone bromide should be reduced from 12 mg to 8 mg (0.4 mL of solution) for those weighing 62 to 114 kg. Patients with severe renal impairment whose weight falls outside the 62 to 114 kg range (see section 5.2) need to reduce their mg/kg dose by 50 %. These patients should use Relistor vials and not the pre-filled syringe. There are no data available from patients with end-stage renal impairment on dialysis, and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2).

There are no data available from patients with severe hepatic impairment (Child-Pugh Class C), and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Paediatric population
The safety and efficacy of methylnaltrexone bromide in children less than 18 years has not been established. No data are available.

Method of administration

Relistor is given as a subcutaneous injection.

It is recommended to rotate injection sites. It is not recommended to inject into areas where the skin is tender, bruised, red, or hard. Areas with scars or stretch marks should be avoided.

The three areas of the body recommended for injection of Relistor are upper legs, abdomen, and upper arms.

Relistor can be injected without regard to food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use of methylnaltrexone bromide in patients with known or suspected mechanical gastrointestinal obstruction, patients at increased risk for recurrent obstruction or in patients with acute surgical abdomen is contraindicated due to the potential for gastrointestinal perforation.

4.4 Special warnings and precautions for use

Severity and worsening symptoms
Patients should be advised to promptly report severe, persistent, and/or worsening symptoms.

If severe or persistent diarrhoea occurs during treatment, patients should be advised not to continue therapy with methylnaltrexone bromide and consult their physician.

Constipation not related to opioid use
The activity of methylnaltrexone bromide has been studied in patients with constipation induced by opioids. Therefore, Relistor should not be used for treatment of patients with constipation not related to opioid use.

Rapid onset of bowel movements

Data from clinical trials suggest treatment with methylnaltrexone bromide can result in the rapid onset (within 30 to 60 minutes on average) of a bowel movement.

Duration of treatment

Opioid-induced constipation in adult patients with advanced illness
Methylnaltrexone bromide treatment has not been studied in adult patients with advanced illness in clinical trials for longer than 4 months, and should therefore only be used for a limited period (see section 5.1).

Hepatic and renal impairment
Methylnaltrexone bromide is not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis (see section 4.2).

Gastrointestinal (GI) conditions and GI perforation
Methylnaltrexone bromide should be used with caution in patients with known or suspected lesions of the GI tract.

Use of methylnaltrexone bromide in patients with colostomy, peritoneal catheter, active diverticular disease or fecal impaction has not been studied. Therefore, Relistor should only be administered with caution in these patients.

Cases of GI perforation have been reported in the postauthorisation period after use of methylnaltrexone bromide in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, pseudo obstruction (Ogilvie's syndrome), diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). The overall risk-benefit profile should be taken into account when using methylnaltrexone bromide in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Patients should be monitored for severe, persistent, or worsening abdominal pain; methylnaltrexone bromide should be discontinued if this symptom occurs.

Opioid withdrawal
Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, vomiting, abdominal pain, palpitations, and blushing have occurred in patients treated with methylnaltrexone bromide. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. This should be taken into account when prescribing methylnaltrexone bromide for such patients.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Methylnaltrexone bromide does not affect the pharmacokinetics of medicinal products metabolised by cytochrome P450 (CYP) isozymes. Methylnaltrexone bromide is minimally metabolised by CYP isozymes. *In vitro* metabolism studies suggest that methylnaltrexone bromide does not inhibit the activity of CYP1A2, CYP2E1, CYP2B6, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of the metabolism of a model CYP2D6 substrate. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.3 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

The organic cation transporter (OCT)-related drug-drug interaction potential between methylnaltrexone bromide and an OCT inhibitor was studied in 18 healthy subjects by comparing the single-dose pharmacokinetic profiles of methylnaltrexone bromide before and after multiple 400 mg doses of cimetidine. The renal clearance of methylnaltrexone bromide was reduced following

multiple-dose administration of cimetidine (from 31 L/h to 18 L/h). However, this resulted in a small reduction in total clearance (from 107 L/h to 95 L/h). Consequently, no meaningful change in AUC of methylnaltrexone bromide, in addition to $C_{max,}$ was observed before and after multiple-dose administration of cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data with the use of methylnaltrexone bromide in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Methylnaltrexone bromide should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether methylnaltrexone bromide is excreted in human breast milk. Animal studies have shown excretion of methylnaltrexone bromide in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with methylnaltrexone bromide should be made, taking into account the benefit of breast-feeding to the child and the benefit of methylnaltrexone bromide therapy to the woman.

Fertility

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

4.7 Effects on ability to drive and use machines

Methylnaltrexone bromide has minor influence on the ability to drive and use machines. Dizziness may occur and this may have an effect on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in all patients exposed to methylnaltrexone bromide during all phases of placebo-controlled studies were abdominal pain, nausea, diarrhoea and flatulence. Generally, these reactions were mild or moderate.

Tabulated list of adverse reactions

The adverse reactions are classified as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Nervous system disorders

Common: Dizziness

Common: opioid-withdrawal-like symptoms (like chills, tremor, rhinorrhea, piloerection, hot flush, palpitation, hyperhidrosis, vomiting, abdominal pain)

Gastrointestinal disorders

Not known: Gastrointestinal perforation (see section 4.4),

Common: Vomiting

Very common: Abdominal pain, nausea, diarrhoea, flatulence

Skin and subcutaneous tissue disorders

Common: Injection site reactions (e.g. stinging, burning, pain , redness, oedema)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

In the event of an overdose, signs and symptoms of orthostatic hypotension should be monitored and reported to a physician. Treatment should be initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Laxatives, Peripheral opioid receptor antagonists, ATC code: A06AH01

Mechanism of action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-receptor. *In vitro* studies have shown methylnaltrexone bromide to be a mu-opioid receptor antagonist (inhibition constant [Ki] = 28 nM), with 8-fold less potency for kappa opioid receptors (Ki = 230 nM) and much reduced affinity for delta opioid receptors.

As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This 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.

Clinical efficacy and safety

Opioid-induced constipation in adult patients with chronic non-cancer pain
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients with chronic non-cancer pain were demonstrated in a randomized, double-blind, placebo-controlled study (Study 3356). In this study, the median patient age was 49 years (range 23-83); 60% were females. The majority of patients had a primary diagnosis of back pain.

Study 3356 compared 4-week treatment regimens of methylnaltrexone bromide 12 mg once daily and methylnaltrexone bromide 12 mg every other day with placebo. The 4-week, double-blind period was followed by an 8-week, open-label period during which methylnaltrexone bromide was to be used as needed, but no more frequently than once daily. A total of 460 patients (methylnaltrexone bromide 12 mg once daily, n=150, methylnaltrexone bromide 12 mg every other day, n=148, placebo, n=162) were treated in the double-blind period. Patients had a history of chronic non-cancer pain and were

taking opioids with stable doses of at least 50 mg of oral morphine equivalents per day. Patients had opioid-induced constipation (< 3 rescue medication-free bowel movements per week during the screening period). Patients were required to discontinue all previous laxative therapy.

The first co=primary endpoint was the proportion of patients having a rescue free bowel movements (RFBMs) within 4 hours of the first dose administration and the second the percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase. A RFBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours.

The proportion of patients having an RFBM within 4 hours of the first dose was 34.2% in the combined methylnaltrexone bromide group versus 9.9% in the placebo group ($p<0.001$). The mean percentage of methylnaltrexone bromide resulting in any RFBM within 4 hours were 28.9% and 30.2% respectively for the once daily and every other day dose groups compared with 9.4% and 9.3% respectively for the corresponding placebo regimen ($p < 0.001$).

The key secondary endpoint of adjusted mean change from baseline in weekly RFBMs was 3.1 in the methylnaltrexone bromide 12 mg once daily treatment group, 2.1 in the methylnaltrexone bromide 12 mg every other day treatment group, and 1.5 in the placebo treatment group during the 4-week double-blind period. The difference between methylnaltrexone bromide 12 mg once daily and placebo of 1.6 RFBMs per week is statistically significant ($p < 0.001$) and clinically meaningful.

Another secondary endpoint evaluated the proportion of patients with ≥3 RFBMs per week during the 4-week double-blind phase. This was achieved in 59% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 61% of those receiving it every other day ($p<0.001$ vs. placebo), and in 38% of the placebo treated patients. A supplementary analysis evaluated the percentage of patients achieving ≥3 complete RFBMs per week and an increase of ≥1 complete RFBMs per week in at least 3 of the 4 treatment weeks. This was achieved in 28.7% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 14.9% of those receiving it every other day ($p=0.012$ vs. placebo), and in 6.2% of the placebo treated patients.

There was no evidence of a differential effect of gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (90 %). Median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients.

There were no clinically relevant changes from baseline in pain scores in either the methylnaltrexone bromide or placebo-treated patients.

The use of methylnaltrexone bromide for treating opioid-induced constipation beyond 48 weeks has not been evaluated in clinical trials.

Opioid-induced constipation in adult patients with advanced illness
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients receiving palliative care was demonstrated in two randomised, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51 % were females. In both studies, patients had advanced terminal illness and limited life expectancy, with the majority having a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had opioid-induced constipation defined as either <3 bowel movements in the preceding week or no bowel movement for >2 days.

Study 301 compared methylnaltrexone bromide given as a single, double-blind, subcutaneous dose of 0.15 mg/kg, or 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label, 4-week dosing period, where methylnaltrexone bromide could be used as needed, no more frequently than 1 dose in a 24-hour period. Throughout both study periods, patients maintained their usual laxative regimen. A total of 154 patients (methylnaltrexone bromide 0.15 mg/kg, n = 47; methylnaltrexone bromide 0.3 mg/kg, n = 55, placebo, n = 52) were treated in the double-blind period.

The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medicinal product. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62 % for 0.15 mg/kg and 58 % for 0.3 mg/kg) than placebo-treated patients (14 %); $p<0.0001$ for each dose versus placebo.

Study 302 compared double-blind, subcutaneous doses of methylnaltrexone bromide given every other day for 2 weeks versus placebo. During the first week (days 1, 3, 5, 7), patients received either methylnaltrexone bromide 0.15 mg/kg or placebo. In the second week, a patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 methylnaltrexone bromide, 71 placebo) patients were analysed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medicinal product and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of medicinal product. Methylnaltrexone bromide-treated patients had a higher rate of laxation within 4 hours of the first dose (48 %) than placebo-treated patients (16 %); $p<0.0001$. Methylnaltrexone bromide-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52 %) than did placebo-treated patients (9 %); $p<0.0001$. Stool consistency was not meaningfully improved in patients who had soft stool at baseline.

In both studies, there was no evidence to suggest differential effects of age or gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (88 %).

Durability of response was demonstrated in Study 302, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide were also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 301, and in two open-label extension studies (301EXT and 302EXT) in which methylnaltrexone bromide was given as needed for up to 4 months (only 8 patients up to this point). A total of 136, 21, and 82 patients received at least one open-label dose in studies 301, 301EXT, and 302EXT, respectively. Relistor was administered every 3.2 days (median dosing interval, with a range of 1-39 days).

The rate of laxation response was maintained throughout the extension studies for those patients who continued treatment.

There was no significant relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

Effect on cardiac repolarisation

In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylnaltrexone bromide (0.15, 0.30 and 0.50 mg/kg), in 207 healthy volunteers, no signal of QT/QTc prolongation or any evidence of an effect on secondary ECG parameters or waveform morphology was detected as compared to placebo and a positive control (orally administered 400 mg moxifloxacin).

5.2 Pharmacokinetic properties

Absorption

Methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours following subcutaneous administration. The C_{max} and area under the plasma concentration-time curve (AUC) increase with dose increase from 0.15 mg/kg to 0.5 mg/kg in a dose-

proportional manner. Absolute bioavailability of a 0.30 mg/kg subcutaneous dose versus a 0.30 mg/kg intravenous dose is 82 %.

Distribution

Methylnaltrexone bromide undergoes moderate tissue distribution. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg. Methylnaltrexone bromide is minimally bound to human plasma proteins (11.0 % to 15.3 %) as determined by equilibrium dialysis.

Biotransformation

Methylnaltrexone bromide is metabolised to a modest extent in humans based on the amount of methylnaltrexone bromide metabolites recovered from excreta. Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulphate appears to be the primary pathway to metabolism. Each of the methyl-6-naltrexol isomers has somewhat less antagonist activity than parent compound, and a low exposure in plasma of approximately 8 % of the drug-related materials. Methylnaltrexone sulphate is an inactive metabolite and present in plasma at a level of approximately 25 % of drug related materials. N-demethylation of methylnaltrexone bromide to produce naltrexone is not significant, accounting for 0.06 % of the administered dose.

Elimination

Methylnaltrexone bromide is eliminated primarily as the unchanged active substance. Approximately half of the dose is excreted in the urine and somewhat less in faeces. The terminal disposition half-life (t1/2) is approximately 8 hours.

Special populations

Hepatic impairment
The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone bromide has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

Renal impairment
In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. The renal clearance of methylnaltrexone bromide decreased with increasing severity of renal impairment. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold; however, this resulted in only a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Paediatric population
No studies have been performed in the paediatric population (see section 4.2).

Elderly population
In a study comparing single and multiple-dose pharmacokinetic profiles of intravenous methylnaltrexone bromide at a dose of 24 mg between healthy, young (18 to 45 years of age n = 10) and elderly (65 years of age and over n = 10) subjects, the effect of age on exposure to methylnaltrexone bromide was found to be minor. The mean steady-state C_{max} and AUC for the elderly were 545 ng/mL and 412 ng•h/mL, approximately 8.1 % and 20 %, respectively, greater than those for young subjects. Therefore, no dose adjustment is recommended based on age.

Gender
No meaningful gender differences have been observed.

Weight
An integrated analysis of pharmacokinetic data from healthy subjects indicated that methylnaltrexone bromide mg/kg dose-adjusted exposure increased as body weight increased. The mean methylnaltrexone bromide exposure at 0.15 mg/kg over a weight range of 38 to 114 kg was 179 (range = 139-240) ng•h/mL. This exposure for the 0.15 mg/kg dose can be achieved with a weight-band-based dose adjustment using an 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg, yielding a mean exposure of 187 (range = 148-220) ng•h/mL. In addition, the analysis showed that 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg correspond to mean doses of 0.16 (range = 0.21-0.13) mg/kg and 0.16 (range = 0.19-0.11) mg/kg, respectively, based on the body weight distribution of patients participating in studies 301 and 302.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Cardiac effects were observed in some non-clinical studies in canines (prolongation of action potentials in Purkinje fibers or prolongation of the QTc interval). The mechanism of this effect is unknown; however, the human cardiac potassium ion channel (hERG) appears not to be involved.

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

There was no evidence of teratogenicity in rats or rabbits. Subcutaneous injections of Relistor at 150/100 mg/kg/day to rats resulted in decreased offspring weights; doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) had no effect on labour, delivery, or offspring survival and growth.

Methylnaltrexone bromide is excreted via the milk of lactating rats.

Studies have been conducted in juvenile rats and dogs. Following intravenous injection of methylnaltrexone bromide, juvenile rats were found to be more sensitive than adult rats to methylnaltrexone-related toxicity. In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs (incidences of convulsions and labored breathing) occurred at dosages (≥ 3 mg/kg/day) and exposures (5.4 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg) that were lower than those that caused similar toxicity in adult rats (20 mg/kg/day). No adverse effects occurred in juvenile rats at 1 mg/kg/day or in adult rats at 5 mg/kg/day (1.6 times and 7.8 times, respectively, the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

Following intravenous injection of methylnaltrexone bromide for 13 weeks, similar methylnaltrexone related toxicity was observed in both juvenile and adult dogs. In adult and juvenile dogs given methylnaltrexone bromide at 20 mg/kg/day, clinical signs indicative of CNS toxicity and prolongation of QTc interval were observed. No adverse effects occurred in either juvenile or adult dogs at a dose of 5 mg/kg/day (44 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium calcium edetate
Glycine hydrochloride

Water for injections
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

After withdrawal in the injection syringe:
Due to light sensitivity, the solution for injection should be used within 24 hours.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the medicinal product in the syringe, see section 6.3.

6.5 Nature and contents of container

Clear, Type I, flint glass, single-use vial, grey butyl rubber stopper, and aluminium overseal with flip-off-cap.

Each vial contains 0.6 mL of solution for injection.

Pack sizes of 1 vial,
2 vials with 2 sterile 1 mL injection syringes with retractable injection needle and 4 alcohol swabs; or
7 vials with 7 sterile 1 mL injection syringes with retractable injection needle and 14 alcohol swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/463/001

EU/1/08/463/002

EU/1/08/463/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2008
Date of latest renewal: 27 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 0.4 mL contains 8 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear solution, colourless to pale-yellow, essentially free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relistor is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.

4.2 Posology and method of administration

Posology

Opioid-induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)
The recommended dose of methylnaltrexone bromide is 12 mg (0.6 mL of solution) subcutaneously, as needed, given as at least 4 doses weekly, up to once daily (7 doses weekly).

In these patients, the treatment with usual laxatives should be stopped when commencing treatment with Relistor (see section 5.1).

The 8 mg pre-filled syringe presentation of Relistor should only be used to treat these patients when existing medical conditions require the dose to be decreased to 8 mg (0.4 mL of solution), see Special Populations.

Opioid-induced constipation in adult patients with advanced illness (palliative care patients)
The recommended dose of methylnaltrexone bromide is 8 mg (0.4 mL of solution) (for patients weighing 38-61 kg) or 12 mg (0.6 mL of solution) (for patients weighing 62-114 kg).

The usual administration schedule is one single dose every other day. Doses may also 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.

Patients weighing less than 38 kg or greater than 114 kg should use Relistor vials because the recommended mg/kg dose cannot be accurately delivered with the pre-filled syringe.

In palliative care patients, Relistor is added to usual laxative treatment (see section 5.1).

Special Populations

Elderly population
No dose adjustment is recommended based on age (see section 5.2).

Patients with renal impairment
In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the dose of methylnaltrexone bromide should be reduced from 12 mg to 8 mg (0.4 mL of solution) for those weighing 62 to 114 kg. Patients with severe renal impairment whose weight falls outside the 62 to 114 kg range (see section 5.2) need to reduce their mg/kg dose by 50 %. These patients should use Relistor vials and not the pre-filled syringe. There are no data available from patients with end-stage renal impairment on dialysis, and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2).

There are no data available from patients with severe hepatic impairment (Child-Pugh Class C), and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Paediatric population
The safety and efficacy of methylnaltrexone bromide in children less than 18 years has not been established. No data are available.

Method of administration

Relistor is given as a subcutaneous injection.

It is recommended to rotate injection sites. It is not recommended to inject into areas where the skin is tender, bruised, red, or hard. Areas with scars or stretch marks should be avoided.

The three areas of the body recommended for injection of Relistor are upper legs, abdomen, and upper arms.

Relistor can be injected without regard to food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use of methylnaltrexone bromide in patients with known or suspected mechanical gastrointestinal obstruction, patients at increased risk for recurrent obstruction or in patients with acute surgical abdomen is contraindicated due to the potential for gastrointestinal perforation.

4.4 Special warnings and precautions for use

Severity and worsening of symptoms
Patients should be advised to promptly report severe, persistent, and/or worsening symptoms.

If severe or persistent diarrhoea occurs during treatment, patients should be advised not to continue therapy with methylnaltrexone bromide and consult their physician.

Constipation not related to opioid use
The activity of methylnaltrexone bromide has been studied in patients with constipation induced by opioids. Therefore, Relistor should not be used for treatment of patients with constipation not related to opioid use.

Rapid onset of bowel movement
Data from clinical trials suggest treatment with methylnaltrexone bromide can result in the rapid onset (within 30 to 60 minutes on average) of a bowel movement.

Duration of treatment

Opioid-induced constipation in adult patients with advanced illness
Methylnaltrexone bromide treatment has not been studied in adult patients with advanced illness in clinical trials for longer than 4 months, and should therefore only be used for a limited period (see section 5.1).

Hepatic or renal impairment
Methylnaltrexone bromide is not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis (see section 4.2).

Gastrointestinal (GI) conditions and GI perforation
Methylnaltrexone bromide should be used with caution in patients with known or suspected lesions of the GI tract.

Use of methylnaltrexone bromide in patients with colostomy, peritoneal catheter, active diverticular disease or fecal impaction has not been studied. Therefore, Relistor should only be administered with caution in these patients.

Cases of GI perforation have been reported in the postauthorisation period after use of methylnaltrexone bromide in patientswith conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, pseudo obstruction (Ogilvie's syndrome), diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). The overall risk-benefit profile should be taken into account when using methylnaltrexone bromide in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Patients should be monitored for severe, persistent, or worsening abdominal pain; methylnaltrexone bromide should be discontinued if this symptom occurs.

Opioid withdrawal
Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, vomiting, abdominal pain, palpitations, and blushing have occurred in patients treated with methylnaltrexone bromide. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. This should be taken into account when prescribing methylnaltrexone bromide for such patients.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Methylnaltrexone bromide does not affect the pharmacokinetics of medicinal products metabolised by cytochrome P450 (CYP) isozymes. Methylnaltrexone bromide is minimally metabolised by CYP isozymes. *In vitro* metabolism studies suggest that methylnaltrexone bromide does not inhibit the activity of CYP1A2, CYP2E1, CYP2B6, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of the metabolism of a model CYP2D6 substrate. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.3 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

The organic cation transporter (OCT)-related drug-drug interaction potential between methylnaltrexone bromide and an OCT inhibitor was studied in 18 healthy subjects by comparing the

single-dose pharmacokinetic profiles of methylnaltrexone bromide before and after multiple 400 mg doses of cimetidine. The renal clearance of methylnaltrexone bromide was reduced following multiple-dose administration of cimetidine (from 31 L/h to 18 L/h). However, this resulted in a small reduction in total clearance (from 107 L/h to 95 L/h). Consequently, no meaningful change in AUC of methylnaltrexone bromide, in addition to C_{max}, was observed before and after multiple-dose administration of cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data with the use of methylnaltrexone bromide in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Methylnaltrexone should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether methylnaltrexone bromide is excreted in human breast milk. Animal studies have shown excretion of methylnaltrexone bromide in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with methylnaltrexone bromide should be made, taking into account the benefit of breast-feeding to the child and the benefit of methylnaltrexone bromide therapy to the woman.

Fertility

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

4.7 Effects on ability to drive and use machines

Methylnaltrexone bromide has minor influence on the ability to drive and use machines. Dizziness may occur, and this may have an effect on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in all patients exposed to methylnaltrexone bromide during all phases of placebo-controlled studies were abdominal pain, nausea, diarrhoea and flatulence. Generally, these reactions were mild or moderate.

Tabulated list of adverse reactions

The adverse reactions are classified as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Nervous system disorders

Common: Dizziness

Common: opioid-withdrawal-like symptoms (like chills, tremor, rhinorrhea, piloerection, hot flush, palpitation, hyperhidrosis, vomiting, abdominal pain)

Gastrointestinal disorders

Not known: Gastrointestinal perforation (see section 4.4)

Common: Vomiting

Very common: Abdominal pain, nausea, diarrhoea, flatulence

Skin and subcutaneous tissue disorders

Common: Injection site reactions (e.g. stinging, burning, pain , redness, oedema)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

In the event of an overdose, signs and symptoms of orthostatic hypotension should be monitored and reported to a physician. Treatment should be initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Laxatives, Peripheral opioid receptor antagonists, ATC code: A06AH01

Mechanism of action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-receptor. *In vitro* studies have shown methylnaltrexone bromide to be a mu-opioid receptor antagonist (inhibition constant [Ki] = 28 nM), with 8-fold less potency for kappa opioid receptors (Ki = 230 nM) and much reduced affinity for delta opioid receptors.

As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This 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.

Clinical efficacy and safety

Opioid-induced constipation in adult patients with chronic non-cancer pain (12 mg dose)
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients with chronic non-cancer pain were demonstrated in a randomized, double-blind, placebo-controlled study (Study 3356). In this study, the median patient age was 49 years (range 23-83); 60% were females. The majority of patients had a primary diagnosis of back pain.

Study 3356 compared 4-week treatment regimens of methylnaltrexone bromide 12 mg once daily and methylnaltrexone bromide 12 mg every other day with placebo. The 4-week, double-blind period was followed by an 8-week, open-label period during which methylnaltrexone bromide was to be used as needed, but no more frequently than once daily. A total of 460 patients (methylnaltrexone bromide

12 mg once daily, n = 150, methylnaltrexone bromide 12 mg every other day, n = 148, placebo, n = 162) were treated in the double-blind period. Patients had a history of chronic non-cancer pain and were taking opioids with stable doses of at least 50 mg of oral morphine equivalents per day. Patients had opioid-induced constipation (< 3 rescue medication-free bowel movements per week during the screening period). Patients were required to discontinue all previous laxative therapy.

The first co-primary endpoint was the proportion of patients having a rescue free bowel movements (RFBMs) within 4 hours of the first dose administration and the second the percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase. A RFBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours.

The proportion of patients having an RFBM within 4 hours of the first dose was 34.2% in the combined methylnaltrexone bromide group versus 9.9% in the placebo group ($p<0.001$). The mean percentage of methylnaltrexone bromide resulting in any RFBM within 4 hours were 28.9% and 30.2% respectively for the once daily and every other day dose groups compared with 9.4% and 9.3% respectively for the corresponding placebo regimen for daily and every other day dosing ($p <0.001$) during the double blind phase.

The key secondary endpoint of adjusted mean change from baseline in weekly RFBMs was 3.1 in the methylnaltrexone bromide 12 mg once daily treatment group, 2.1 in the methylnaltrexone bromide 12 mg every other day treatment group, and 1.5 in the placebo treatment group during the 4-week double-blind period. The difference between methylnaltrexone bromide 12 mg once daily and placebo of 1.6 RFBMs per week is statistically significant ($p < 0.001$) and clinically meaningful.

Another secondary endpoint evaluated the proportion of patients with ≥3 RFBMs per week during the 4-week double-blind phase. This was achieved in 59% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 61% of those receiving it every other day ($p<0.001$ vs. placebo), and in 38% of the placebo treated patients. A supplementary analysis evaluated a hard endpoint of the percentage of patients achieving ≥3 complete RFBMs per week and an increase of ≥1 complete RFBMs per week in at least 3 of the 4 treatment weeks. This was achieved in 28.7% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 14.9% of those receiving it every other day ($p=0.012$ vs. placebo), and in 6.2% of the placebo treated patients.

There was no evidence of a differential effect of gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (90 %). Median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients.

There were no clinically relevant changes from baseline in pain scores in either the methylnaltrexone bromide or placebo-treated patients.

The use of methylnaltrexone bromide for treating opioid-induced constipation beyond 48 weeks has not been evaluated in clinical trials.

Opioid-induced constipation in adult patients with advanced illness
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients receiving palliative care was demonstrated in two randomised, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51 % were females. In both studies, patients had advanced terminal illness and limited life expectancy, with the majority having a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had opioid-induced constipation defined as either <3 bowel movements in the preceding week or no bowel movement for >2 days.

Study 301 compared methylnaltrexone bromide given as a single, double-blind, subcutaneous dose of 0.15 mg/kg, or 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label, 4-week dosing period, where methylnaltrexone bromide could be used as needed, no more frequently

than 1 dose in a 24-hour period. Throughout both study periods, patients maintained their usual laxative regimen. A total of 154 patients (methylnaltrexone bromide 0.15 mg/kg, n = 47; methylnaltrexone bromide 0.3 mg/kg, n = 55, placebo, n = 52) were treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medicinal product. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62 % for 0.15 mg/kg and 58 % for 0.3 mg/kg) than placebo-treated patients (14 %); $p<0.0001$ for each dose versus placebo.

Study 302 compared double-blind, subcutaneous doses of methylnaltrexone bromide given every other day for 2 weeks versus placebo. During the first week (days 1, 3, 5, 7), patients received either methylnaltrexone bromide 0.15 mg/kg or placebo. In the second week, a patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 methylnaltrexone bromide, 71 placebo) patients were analysed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medicinal product and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of medicinal product. Methylnaltrexone bromide-treated patients had a higher rate of laxation within 4 hours of the first dose (48 %) than placebo-treated patients (16 %); $p<0.0001$. Methylnaltrexone bromide-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52 %) than did placebo-treated patients (9 %); $p<0.0001$. Stool consistency was not meaningfully improved in patients who had soft stool at baseline.

In both studies, there was no evidence to suggest differential effects of age or gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (88 %).

Durability of response was demonstrated in Study 302, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide were also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 301, and in two open-label extension studies (301EXT and 302EXT) in which methylnaltrexone bromide was given as needed for up to 4 months (only 8 patients up to this point). A total of 136, 21, and 82 patients received at least one open-label dose in studies 301, 301EXT, and 302EXT, respectively. Relistor was administered every 3.2 days (median dosing interval, with a range of 1-39 days).

The rate of laxation response was maintained throughout the extension studies for those patients who continued treatment.

There was no significant relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

Effect on cardiac repolarisation

In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylnaltrexone bromide (0.15, 0.30 and 0.50 mg/kg), in 207 healthy volunteers, no signal of QT/QTc prolongation or any evidence of an effect on secondary ECG parameters or waveform morphology was detected as compared to placebo and a positive control (orally administered 400 mg moxifloxacin).

5.2 Pharmacokinetic properties

Absorption

Methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours following subcutaneous administration. The C_{max} and area under the plasma concentration-time curve (AUC) increase with dose increase from 0.15 mg/kg to 0.5 mg/kg in a dose-proportional manner. Absolute bioavailability of a 0.30 mg/kg subcutaneous dose versus a 0.30 mg/kg intravenous dose is 82 %.

Distribution

Methylnaltrexone bromide undergoes moderate tissue distribution. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg. Methylnaltrexone bromide is minimally bound to human plasma proteins (11.0 % to 15.3 %) as determined by equilibrium dialysis.

Biotransformation

Methylnaltrexone bromide is metabolised to a modest extent in humans based on the amount of methylnaltrexone bromide metabolites recovered from excreta. Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulphate appears to be the primary pathway to metabolism. Each of the methyl-6-naltrexol isomers has somewhat less antagonist activity than parent compound, and a low exposure in plasma of approximately 8 % of the drug-related materials. Methylnaltrexone sulphate is an inactive metabolite and present in plasma at a level of approximately 25 % of drug related materials. N-demethylation of methylnaltrexone bromide to produce naltrexone is not significant, accounting for 0.06 % of the administered dose.

Elimination

Methylnaltrexone bromide is eliminated primarily as the unchanged active substance. Approximately half of the dose is excreted in the urine and somewhat less in faeces. The terminal disposition half-life (t1/2) is approximately 8 hours.

Special populations

Hepatic impairment
The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone bromide has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

Renal impairment
In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. The renal clearance of methylnaltrexone bromide decreased with increasing severity of renal impairment. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold; however, this resulted in only a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Paediatric population
No studies have been performed in the paediatric population (see section 4.2).

Elderly population
In a study comparing single and multiple-dose pharmacokinetic profiles of intravenous methylnaltrexone bromide at a dose of 24 mg between healthy, young (18 to 45 years of age n = 10) and elderly (65 years of age and over n = 10) subjects, the effect of age on exposure to methylnaltrexone bromide was found to be minor. The mean steady-state C_{max} and AUC for the elderly were 545 ng/mL and 412 ng•h/mL, approximately 8.1 % and 20 %, respectively, greater than those for young subjects. Therefore, no dose adjustment is recommended based on age.

Gender
No meaningful gender differences have been observed.

Weight
An integrated analysis of pharmacokinetic data from healthy subjects indicated that methylnaltrexone bromide mg/kg dose-adjusted exposure increased as body weight increased. The mean methylnaltrexone bromide exposure at 0.15 mg/kg over a weight range of 38 to 114 kg was 179 (range = 139-240) ng•h/mL. This exposure for the 0.15 mg/kg dose can be achieved with a weight-band-based dose adjustment using an 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg, yielding a mean exposure of 187 (range = 148-220) ng•h/mL. In addition, the analysis showed that 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg correspond to mean doses of 0.16 (range = 0.21-0.13) mg/kg and 0.16 (range = 0.19-0.11) mg/kg, respectively, based on the body weight distribution of patients participating in studies 301 and 302.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Cardiac effects were observed in some non-clinical studies in canines (prolongation of action potentials in Purkinje fibers or prolongation of the QTc interval). The mechanism of this effect is unknown; however, the human cardiac potassium ion channel (hERG) appears not to be involved.

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

There was no evidence of teratogenicity in rats or rabbits. Subcutaneous injections of Relistor at 150/100 mg/kg/day to rats resulted in decreased offspring weights; doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) had no effect on labour, delivery, or offspring survival and growth.

Methylnaltrexone bromide is excreted via the milk of lactating rats.

Studies have been conducted in juvenile rats and dogs. Following intravenous injection of methylnaltrexone bromide, juvenile rats were found to be more sensitive than adult rats to methylnaltrexone-related toxicity. In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs (incidences of convulsions and labored breathing) occurred at dosages (≥ 3 mg/kg/day) and exposures (5.4 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg) that were lower than those that caused similar toxicity in adult rats (20 mg/kg/day). No adverse effects occurred in juvenile rats at 1 mg/kg/day or in adult rats at 5 mg/kg/day (1.6 times and 7.8 times, respectively, the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

Following intravenous injection of methylnaltrexone bromide for 13 weeks, similar methylnaltrexone related toxicity was observed in both juvenile and adult dogs. In adult and juvenile dogs given methylnaltrexone bromide at 20 mg/kg/day, clinical signs indicative of CNS toxicity and prolongation of QTc interval were observed. No adverse effects occurred in either juvenile or adult dogs at a dose of 5 mg/kg/day (44 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium calcium edetate
Glycine hydrochloride
Water for injections
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 30ºC.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each pre-filled syringe contains 0.4 mL of solution for injection.

Pre-filled syringe of clear type I glass with stainless-steel needle, plastic plunger, and polypropylene rigid needle cover.

Pack sizes of 4, 7, 8 and 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/463/004

EU/1/08/463/005

EU/1/08/463/006

EU/1/08/463/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2008
Date of latest renewal: 27 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 0.6 mL contains 12 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear solution, colourless to pale-yellow, essentially free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relistor is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.

4.2 Posology and method of administration

Posology

Opioid-induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)
The recommended dose of methylnaltrexone bromide is 12 mg (0.6 mL of solution) subcutaneously, as needed, given as at least 4 doses weekly up to once daily (7 doses weekly).

In these patients, the treatment with usual laxatives should be stopped when commencing treatment with Relistor (see section 5.1).

Opioid-induced constipation in adult patients with advanced illness (palliative care patients)
The recommended dose of methylnaltrexone bromide is 8 mg (0.4 mL of solution) (for patients weighing 38-61 kg) or 12 mg (0.6 mL of solution) (for patients weighing 62-114 kg).

The usual administration schedule is one single dose every other day. Doses may also 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.

Patients weighing less than 38 kg or greater than 114 kg should use Relistor vials because the recommended mg/kg dose cannot be accurately delivered with the pre-filled syringe.

In palliative care patients, Relistor is added to usual laxative treatment (see section 5.1).

Special populations

Elderly population
No dose adjustment is recommended based on age (see section 5.2).

Patients with renal impairment
In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the dose of methylnaltrexone bromide should be reduced from 12 mg to 8 mg (0.4 mL of solution) for those weighing 62 to 114 kg. Patients with severe renal impairment whose weight falls outside the 62 to 114 kg range (see section 5.2) need to reduce their mg/kg dose by 50 %. These patients should use Relistor vials and not the pre-filled syringe. There are no data available from patients with end-stage renal impairment on dialysis, and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2).

There are no data available from patients with severe hepatic impairment (Child-Pugh Class C), and methylnaltrexone bromide is not recommended in these patients (see section 4.4).

Paediatric population
The safety and efficacy of Relistor in children less than 18 years has not been established. No data are available.

Method of administration

Relistor is given as a subcutaneous injection.

It is recommended to rotate injection sites. It is not recommended to inject into areas where the skin is tender, bruised, red, or hard. Areas with scars or stretch marks should be avoided.

The three areas of the body recommended for injection of Relistor are upper legs, abdomen, and upper arms.

Relistor can be injected without regard to food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use of methylnaltrexone bromide in patients with known or suspected mechanical gastrointestinal obstruction, patients at increased risk for recurrent obstruction or in patients with acute surgical abdomen is contraindicated due to the potential for gastrointestinal perforation.

4.4 Special warnings and precautions for use

Severity and worsening of symptoms
Patients should be advised to promptly report severe, persistent, and/or worsening symptoms.

If severe or persistent diarrhoea occurs during treatment, patients should be advised not to continue therapy with methylnaltrexone bromide and consult their physician.

Constipation not related to opioid use
The activity of methylnaltrexone bromide has been studied in patients with constipation induced by opioids. Therefore, Relistor should not be used for treatment of patients with constipation not related to opioid use.

Rapid onset of bowel movements
Data from clinical trials suggest treatment with methylnaltrexone bromide can result in the rapid onset (within 30 to 60 minutes on average) of a bowel movement.

Duration of treatment

Opioid-induced constipation in adult patients with advanced illness
Methylnaltrexone bromide treatment has not been studied in adult patients with advanced illness in clinical trials for longer than 4 months, and should therefore only be used for a limited period (see section 5.1).

Hepatic or renal impairment
Methylnaltrexone bromide is not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis (see section 4.2).

Gastrointestinal (GI) conditions and GI perforation
Methylnaltrexone bromide should be used with caution in patients with known or suspected lesions of the GI tract.

Use of methylnaltrexone bromide in patients with colostomy, peritoneal catheter, active diverticular disease or fecal impaction has not been studied. Therefore, Relistor should only be administered with caution in these patients.

Cases of GI perforation have been reported in the postauthorisation period after use of methylnaltrexone bromide in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, pseudo obstruction (Ogilvie's syndrome), diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). The overall risk-benefit profile should be taken into account when using methylnaltrexone bromide in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Patients should be monitored for severe, persistent, or worsening abdominal pain; methylnaltrexone bromide should be discontinued if this symptom occurs.

Opioid withdrawal
Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, vomiting, abdominal pain, palpitations, and blushing have occurred in patients treated with methylnaltrexone bromide. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. This should be taken into account when prescribing methylnaltrexone bromide for such patients.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Methylnaltrexone bromide does not affect the pharmacokinetics of medicinal products metabolised by cytochrome P450 (CYP) isozymes. Methylnaltrexone bromide is minimally metabolised by CYP isozymes. *In vitro* metabolism studies suggest that methylnaltrexone bromide does not inhibit the activity of CYP1A2, CYP2E1, CYP2B6, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of the metabolism of a model CYP2D6 substrate. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.3 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

The organic cation transporter (OCT)-related drug-drug interaction potential between methylnaltrexone bromide and an OCT inhibitor was studied in 18 healthy subjects by comparing the single-dose pharmacokinetic profiles of methylnaltrexone bromide before and after multiple 400 mg doses of cimetidine. The renal clearance of methylnaltrexone bromide was reduced following multiple-dose administration of cimetidine (from 31 L/h to 18 L/h). However, this resulted in a small reduction in total clearance (from 107 L/h to 95 L/h). Consequently, no meaningful change in AUC of

methylnaltrexone bromide, in addition to C_{max}, was observed before and after multiple-dose administration of cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data with the use of methylnaltrexone bromide in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Methylnaltrexone bromide should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether methylnaltrexone bromide is excreted in human breast milk. Animal studies have shown excretion of methylnaltrexone bromide in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with methylnaltrexone bromide should be made, taking into account the benefit of breast-feeding to the child and the benefit of methylnaltrexone bromide therapy to the woman.

Fertility

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

4.7 Effects on ability to drive and use machines

Methylnaltrexone bromide has minor influence on the ability to drive and use machines. Dizziness may occur, and this may have an effect on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in all patients exposed to methylnaltrexone bromide during all phases of placebo-controlled studies were abdominal pain, nausea, diarrhoea and flatulence. Generally, these reactions were mild or moderate.

Tabulated list of adverse reactions

The adverse reactions are classified as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Nervous system disorders

Common: Dizziness

Common: opioid-withdrawal-like symptoms (like chills, tremor, rhinorrhea, piloerection, hot flush, palpitation, hyperhidrosis, vomiting, abdominal pain)

Gastrointestinal disorders

Not known: Gastrointestinal perforation (see section 4.4)

Common: Vomiting

Very common: Abdominal pain, nausea, diarrhoea, flatulence

Skin and subcutaneous tissue disorders

Common: Injection site reactions (e.g. stinging, burning, pain , redness, oedema)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

In the event of an overdose, signs and symptoms of orthostatic hypotension should be monitored and reported to a physician. Treatment should be initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Laxatives, Peripheral opioid receptor antagonists, ATC code: A06AH01

Mechanism of action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-receptor. *In vitro* studies have shown methylnaltrexone bromide to be a mu-opioid receptor antagonist (inhibition constant [Ki] = 28 nM), with 8-fold less potency for kappa opioid receptors (Ki = 230 nM) and much reduced affinity for delta opioid receptors.

As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This 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.

Clinical efficacy and safety

Opioid-induced constipation in adult patients with chronic non-cancer pain
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients with chronic non-cancer pain were demonstrated in a randomized, double-blind, placebo-controlled study (Study 3356). In this study, the median patient age was 49 years (range 23-83); 60% were females. The majority of patients had a primary diagnosis of back pain.

Study 3356 compared 4-week treatment regimens of methylnaltrexone bromide 12 mg once daily and methylnaltrexone bromide 12 mg every other day with placebo. The 4-week, double-blind period was followed by an 8-week, open-label period during which methylnaltrexone bromide was to be used as needed, but no more frequently than once daily. A total of 460 patients (methylnaltrexone bromide 12 mg once daily, n=150, methylnaltrexone bromide 12 mg every other day, n=148, placebo, n=162) were treated in the double-blind period. Patients had a history of chronic non-cancer pain and were taking opioids with stable doses of at least 50 mg of oral morphine equivalents per day. Patients had been receiving opioid therapy for pain (median daily baseline oral morphine equivalent

dose = 160 mg) and had opioid-induced constipation (<3 rescue medication-free bowel movements per week during the screening period). Patients were required to discontinue all previous laxative therapy.

The first co-primary endpoint was the proportion of patients having a rescue free bowel movements (RFBMs) within 4 hours of the first dose administration and the second the percentage of active injections resulting in any RFBM within 4 hours during the double-blind phase. A RFBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours.

The proportion of patients having an RFBM within 4 hours of the first dose was 34.2% in the combined methylnaltrexone bromide group versus 9.9% in the placebo group ($p<0.001$). The mean percentage of methylnaltrexone bromide resulting in any RFBM within 4 hours were 28.9% and 30.2% respectively for the once daily and every other day dose groups compared with 9.4% and 9.3% respectively for the corresponding placebo regimen ($p <0.001$).

The key secondary endpoint of adjusted mean change from baseline in weekly RFBMs was 3.1 in the methylnaltrexone bromide 12 mg once daily treatment group, 2.1 in the methylnaltrexone bromide 12 mg every other day treatment group, and 1.5 in the placebo treatment group during the 4-week double-blind period. The difference between methylnaltrexone bromide 12 mg once daily and placebo of 1.6 RFBMs per week is statistically significant ($p < 0.001$) and clinically meaningful.

Another secondary endpoint evaluated the proportion of patients with ≥3 RFBMs per week during the 4-week double-blind phase. This was achieved in 59% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 61% of those receiving it every other day ($p<0.001$ vs. placebo), and in 38% of the placebo treated patients. A supplementary analysis evaluated a hard endpoint of the percentage of patients achieving ≥3 complete RFBS per week and an increase of ≥1 complete RFBMs per week in at least 3 of the 4 treatment weeks. This was achieved in 28.7% of the patients in the group receiving daily methylnaltrexone 12 mg ($p<0.001$ vs. placebo), in 14.9% of those receiving it every other day ($p=0.012$ vs. placebo), and in 6.2% of the placebo treated patients.

There was no evidence of a differential effect of gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (90 %). Median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients.

There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

The use of methylnaltrexone bromide for treating opioid-induced constipation beyond 48 weeks has not been evaluated in clinical trials.

Opioid-induced constipation in adult patients with advanced illness
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients receiving palliative care was demonstrated in two randomised, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51 % were females. In both studies, patients had advanced terminal illness and limited life expectancy, with the majority having a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had opioid-induced constipation defined as either <3 bowel movements in the preceding week or no bowel movement for >2 days.

Study 301 compared methylnaltrexone bromide given as a single, double-blind, subcutaneous dose of 0.15 mg/kg, or 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label, 4-week dosing period, where methylnaltrexone bromide could be used as needed, no more frequently than 1 dose in a 24-hour period. Throughout both study periods, patients maintained their usual laxative regimen. A total of 154 patients (methylnaltrexone bromide 0.15 mg/kg, n = 47; methylnaltrexone bromide 0.3 mg/kg, n = 55, placebo, n = 52) were treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the

double-blind dose of study medicinal product. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62 % for 0.15 mg/kg and 58 % for 0.3 mg/kg) than placebo-treated patients (14 %); p<0.0001 for each dose versus placebo.

Study 302 compared double-blind, subcutaneous doses of methylnaltrexone bromide given every other day for 2 weeks versus placebo. During the first week (days 1, 3, 5, 7), patients received either methylnaltrexone bromide 0.15 mg/kg or placebo. In the second week, a patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 methylnaltrexone bromide, 71 placebo) patients were analysed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medicinal product and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of medicinal product. Methylnaltrexone bromide-treated patients had a higher rate of laxation within 4 hours of the first dose (48 %) than placebo-treated patients (16 %); p<0.0001. Methylnaltrexone bromide-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52 %) than did placebo-treated patients (9 %); p<0.0001. Stool consistency was not meaningfully improved in patients who had soft stool at baseline.

In both studies, there was no evidence to suggest differential effects of age or gender on safety or efficacy. The effect on race could not be analysed because the study population was predominantly Caucasian (88 %).

Durability of response was demonstrated in Study 302, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide were also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 301, and in two open-label extension studies (301EXT and 302EXT) in which methylnaltrexone bromide was given as needed for up to 4 months (only 8 patients up to this point). A total of 136, 21, and 82 patients received at least one open-label dose in studies 301, 301EXT, and 302EXT, respectively. Relistor was administered every 3.2 days (median dosing interval, with a range of 1-39 days).

The rate of laxation response was maintained throughout the extension studies for those patients who continued treatment.

There was no significant relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

Effect on cardiac repolarisation

In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylnaltrexone bromide (0.15, 0.30 and 0.50 mg/kg), in 207 healthy volunteers, no signal of QT/QTc prolongation or any evidence of an effect on secondary ECG parameters or waveform morphology was detected as compared to placebo and a positive control (orally administered 400 mg moxifloxacin).

5.2 Pharmacokinetic properties

Absorption

Methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours following subcutaneous administration. The C_{max} and area under the plasma concentration-time curve (AUC) increase with dose increase from 0.15 mg/kg to 0.5 mg/kg in a dose-

proportional manner. Absolute bioavailability of a 0.30 mg/kg subcutaneous dose versus a 0.30 mg/kg intravenous dose is 82 %.

Distribution

Methylnaltrexone bromide undergoes moderate tissue distribution. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg. Methylnaltrexone bromide is minimally bound to human plasma proteins (11.0 % to 15.3 %) as determined by equilibrium dialysis.

Biotransformation

Methylnaltrexone bromide is metabolised to a modest extent in humans based on the amount of methylnaltrexone bromide metabolites recovered from excreta. Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulphate appears to be the primary pathway to metabolism. Each of the methyl-6-naltrexol isomers has somewhat less antagonist activity than parent compound, and a low exposure in plasma of approximately 8 % of the drug-related materials. Methylnaltrexone sulphate is an inactive metabolite and present in plasma at a level of approximately 25 % of drug related materials. N-demethylation of methylnaltrexone bromide to produce naltrexone is not significant, accounting for 0.06 % of the administered dose.

Elimination

Methylnaltrexone bromide is eliminated primarily as the unchanged active substance. Approximately half of the dose is excreted in the urine and somewhat less in faeces. The terminal disposition half-life (t1/2) is approximately 8 hours.

Special populations

Hepatic impairment
The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone bromide has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

Renal impairment
In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. The renal clearance of methylnaltrexone bromide decreased with increasing severity of renal impairment. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold; however, this resulted in only a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Paediatric population
No studies have been performed in the paediatric population (see section 4.2).

Elderly population
In a study comparing single and multiple-dose pharmacokinetic profiles of intravenous methylnaltrexone bromide at a dose of 24 mg between healthy, young (18 to 45 years of age n = 10) and elderly (65 years of age and over n = 10) subjects, the effect of age on exposure to methylnaltrexone bromide was found to be minor. The mean steady-state C_{max} and AUC for the elderly were 545 ng/mL and 412 ng•h/mL, approximately 8.1 % and 20 %, respectively, greater than those for young subjects. Therefore, no dose adjustment is recommended based on age.

Gender
No meaningful gender differences have been observed.

Weight
An integrated analysis of pharmacokinetic data from healthy subjects indicated that methylnaltrexone bromide mg/kg dose-adjusted exposure increased as body weight increased. The mean methylnaltrexone bromide exposure at 0.15 mg/kg over a weight range of 38 to 114 kg was 179 (range = 139-240) ng•h/mL. This exposure for the 0.15 mg/kg dose can be achieved with a weight-band-based dose adjustment using an 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg, yielding a mean exposure of 187 (range = 148-220) ng•h/mL. In addition, the analysis showed that 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg correspond to mean doses of 0.16 (range = 0.21-0.13) mg/kg and 0.16 (range = 0.19-0.11) mg/kg, respectively, based on the body weight distribution of patients participating in studies 301 and 302.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Cardiac effects were observed in some non-clinical studies in canines (prolongation of action potentials in Purkinje fibers or prolongation of the QTc interval). The mechanism of this effect is unknown; however, the human cardiac potassium ion channel (hERG) appears not to be involved.

Subcutaneous injections of Relistor at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

There was no evidence of teratogenicity in rats or rabbits. Subcutaneous injections of Relistor at 150/100 mg/kg/day to rats resulted in decreased offspring weights; doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) had no effect on labour, delivery, or offspring survival and growth.

Methylnaltrexone bromide is excreted via the milk of lactating rats.

Studies have been conducted in juvenile rats and dogs. Following intravenous injection of methylnaltrexone bromide, juvenile rats were found to be more sensitive than adult rats to methylnaltrexone-related toxicity. In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs (incidences of convulsions and labored breathing) occurred at dosages (≥ 3 mg/kg/day) and exposures (5.4 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg) that were lower than those that caused similar toxicity in adult rats (20 mg/kg/day). No adverse effects occurred in juvenile rats at 1 mg/kg/day or in adult rats at 5 mg/kg/day (1.6 times and 7.8 times, respectively, the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

Following intravenous injection of methylnaltrexone bromide for 13 weeks, similar methylnaltrexone related toxicity was observed in both juvenile and adult dogs. In adult and juvenile dogs given methylnaltrexone bromide at 20 mg/kg/day, clinical signs indicative of CNS toxicity and prolongation of QTc interval were observed. No adverse effects occurred in either juvenile or adult dogs at a dose of 5 mg/kg/day (44 times the exposure {AUC} in adult humans at a subcutaneous dose of 0.15 mg/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium calcium edetate
Glycine hydrochloride

Water for injections
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 30ºC.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each pre-filled syringe contains 0.6 mL of solution for injection.

Pre-filled syringe of clear type I glass with stainless-steel needle, plastic plunger, and polypropylene rigid needle cover.

Pack sizes of 4, 7, 8 and 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/463/008

EU/1/08/463/009

EU/1/08/463/010

EU/1/08/463/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2008
Date of latest renewal: 27 May 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bausch Health Poland Sp. z o. o.,
ul. Kosztowska 21,
41-409 Mysłowice,
Poland

Przedsiębiorstwo Farmaceutyczne Jelfa SA
ul. Wincentego Pola 21
58-500 Jelenia Góra,
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (VIAL PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg/0.6 mL solution for injection
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of 0.6 mL contains 12 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 vial of 0.6 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg/0.6 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (VIAL PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg/0.6 mL solution for injection
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of 0.6 mL contains 12 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

2 vials of 0.6 mL
2 sterile 1 mL injection syringes with retractable injection needle
4 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg/0.6 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (VIAL PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg/0.6 mL solution for injection
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of 0.6 mL contains 12 mg of methylnaltrexone bromide.
One mL of solution contains 20 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

7 vials of 0.6 mL
7 sterile 1 mL injection syringes with retractable injection needle
14 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg/0.6 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.4 mL contains 8 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

4 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.4 mL contains 8 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.4 mL contains 8 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

8 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.4 mL contains 8 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.6 mL contains 12 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

4 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.6 mL contains 12 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.6 mL contains 12 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

8 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Citywest Business Campus
Dublin 24, D24PPT3
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe of 0.6 mL contains 12 mg of methylnaltrexone bromide.

3. LIST OF EXCIPIENTS

Sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

10 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/08/463/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RELISTOR 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABEL TEXT FOR TRAY LIDDING (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg solution for injection in pre-filled syringe

Methylnaltrexone bromide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use (SC)

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

0.6 mL of solution (12 mg methylnaltrexone bromide)

Read the package leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Relistor 8 mg injection
Methylnaltrexone bromide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABEL TEXT FOR TRAY LIDDING (PRE-FILLED SYRINGE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 8 mg solution for injection in pre-filled syringe

Methylnaltrexone bromide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use (SC)

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

0.4 mL of solution (8 mg methylnaltrexone bromide)

Read the package leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Relistor 12 mg Injection
Methylnaltrexone bromide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABEL TEXT FOR INTERMEDIATE CARTON (VIAL PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg/0.6 mL solution for injection

Methylnaltrexone bromide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bausch Health Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Keep the vial in the outer carton in order to protect from light.

Syringe Needle Retracts After Use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Relistor 12 mg/0.6 mL solution for injection
Methylnaltrexone bromide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 mL of solution (12 mg methylnaltrexone bromide)

6. OTHER

Keep the vial in the outer carton in order to protect from light.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Relistor 12 mg/0.6 mL solution for injection
Methylnaltrexone bromide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Relistor is and what it is used for

Relistor contains an active substance called methylnaltrexone bromide which acts by blocking the side effects of opioid pain medicines that affect the bowel.

It treats constipation that is caused by medicines for moderate to severe pain called opioids (for example morphine or codeine). It is used for patients when other medicines for constipation, called laxatives, have not worked well enough. Opioids are prescribed by your doctor. Your doctor will tell you whether you should stop or continue taking your usual laxatives when you start using this medicine.

This medicine is for use in adults (aged 18 and over).

2. What you need to know before you use Relistor

Do not use Relistor
- If you are allergic to methylnaltrexone bromide or any of the other ingredients of this medicine (listed in section 6).
- If you or your doctor know that your bowels were or are obstructed or your bowels are in a state where there is an immediate need for surgical intervention (which has to be diagnosed by your doctor).

Warnings and precautions
Talk to your doctor or pharmacist before using Relistor.
- If you have severe stomach symptoms which continue or get worse, contact your doctor immediately because these could be symptoms of a hole developing in the bowel wall (intestinal perforation). See section 4.
- If you have Crohn´s disease or gastrointestinal ulcers
- If you feel sick, vomit, shiver, sweat, have belly pain and/or feel a fast heart beat shortly after taking Relistor talk to your doctor
- If you have severe liver or kidney disease.

- If you develop severe or persistent diarrhoea (passing of frequent watery stools), discontinue therapy and contact your doctor immediately.
- It is important to be near a toilet with assistance available if necessary, since bowel movement may happen within 30 minutes after injection of the medicine.
- Please talk to your doctor if you experience stomach ache which continues, nausea (feeling sick) or vomiting (being sick) that is new or becomes worse.
- Please also talk to your doctor if you have a colostomy, a tube in your abdomen (peritoneal catheter), or suffer from diverticular disease or faecal impaction as this medicine should be used carefully in these circumstances.
- If you are receiving supportive care for your advanced illness, this medicine will only be used for a limited period of time, which will usually be less than 4 months.
- This medicine should not be used for treatment of patients with constipation which is not related to opioid use. If you have suffered from constipation before you had to take opioids (for pain), please talk to your doctor.

Children and adolescents
Do not give this medicine to children and adolescents under the age of 18 because the potential risks and benefits are not known.

Other medicines and Relistor
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may allow you to take other medicines, including those used for constipation.

Pregnancy and breast-feeding
The effects of methylnaltrexone bromide in pregnant women are not known. Your doctor will decide if you can use Relistor if you are pregnant.

Women using this medicine should not breast-feed, since it is not known if methylnaltrexone bromide passes into human breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Dizziness is a common side effect of this medicine. This may have an effect on your ability to drive and use machines.

Important information about some of the ingredients of Relistor
This medicine contains less than 1 mmol sodium (23 mg) per dose i.e., essentially “sodium free.”

3. How to use Relistor

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for patients with long-term pain (except patients receiving supportive care for advanced illness) is 12 mg methylnalrexone bromide (0.6 mL of solution) given as an injection under the skin, as needed, but at least given 4-times a week and up to once a day (7 times a week).

The recommended dose for patients receiving supportive care for advanced illness is 8 mg methylnaltrexone bromide (0.4 mL of solution) for patients weighing 38-61 kg or 12 mg (0.6 mL of solution) for patients weighing 62-114 kg. The dose is given every 48 hours (every two days) as an injection under the skin.

Your doctor will determine your dose.

This medicine is given by an injection under the skin (by subcutaneous injection) in either (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (if not self-injecting). (See INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR at the end of this leaflet.)

You may have a bowel movement within a few minutes to a few hours of the injection; therefore, it is recommended to have a toilet facility or bedpan near you.

If you use more Relistor than you should
If you have used more this medicine than you should (either by injecting too much on a single occasion or by using more than one injection in 24 hours), you may feel dizzy when standing up, so talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Relistor
If you forget a dose, talk to your doctor or pharmacist as soon as possible. Do not take a double dose to make up for a forgotten dose.

If you stop using Relistor
You should talk to a doctor or pharmacist if you want to stop using this medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Cases of a hole developing in the bowel wall (gastrointestinal perforation) have been reported in patients using Relistor. How often this happens is not known from the data that is available. If you get a stomach ache that is either severe or will not go away, stop taking this medicine and call your doctor straight away.

The following side effects are very common and may affect more than 1 in 10 people. If you experience any of these side effects, which are either severe or will not go away, you should talk to your doctor:

- Abdominal pain (stomach ache)
- Nausea (feeling sick)
- Diarrhoea (passing of frequent watery stools)
- Flatulence (passing wind)

Other common side effects that may affect up to 1 in 10 people are:

- Dizziness (light-headed)
- Opioid-withdrawal-like symptoms (any of the following: feeling cold, shivering, runny nose, sweating, hair standing on end, blushing, fast heart beat)
- Reaction at the site of injection (e.g., stinging, burning, pain, redness, oedema)
- Vomiting

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Relistor

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions.

Keep the vial in the outer carton in order to protect from light.

Only use this medicine if the solution is clear, colourless to pale yellow, and does not contain flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Relistor contains
- The active substance is methylnaltrexone bromide. Each vial of 0.6 mL contains 12 mg methylnaltrexone bromide. One mL of solution contains 20 mg methylnaltrexone bromide.
- The other ingredients are sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH) and sodium hydroxide (to adjust pH).

What Relistor looks like and contents of the pack

Relistor is a solution for injection. It is clear, colourless to pale yellow, and does not contain flakes or particles.

Each vial contains 0.6 mL of solution.

Packs of more than one vial contain inner cartons consisting of: one vial, one 1 mL injection syringe with retractable injection needle, and two alcohol swabs.

The following packs are available:

Single vial

Pack containing 2 vials, 2 injection syringes with retractable injection needle, and 4 alcohol swabs (i.e. 2 inner cartons).

Pack containing 7 vials, 7 injection syringes with retractable injection needle, and 14 alcohol swabs (i.e. 7 inner cartons).

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

Manufacturer

Bausch Health Poland Sp. z o. o.,
ul. Kosztowska 21,
41-409 Mysłowice,
Poland
Przedsiębiorstwo Farmaceutyczne Jelfa SA
ul. Wincentego Pola 21
58-500 Jelenia Góra,
Poland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

PATIENT CHECKLIST

This section contains important questions that you will need to answer before you take Relistor, and during treatment with Relistor.

If you answer No to any of the following questions during the course of treatment with your medicine, please contact your doctor, nurse or pharmacist.

1. Are you receiving opioid therapy (for example morphine or codeine) for your illness?
2. Has it been 48 hours or longer since your last bowel movement?
3. Are you familiar with the technique of self injection or have you discussed this with your doctor (or nurse or pharmacist)?
4. Are you mobile enough to reach the toilet, or do you have a caregiver looking after you who can help?
5. Do you have a contact number for your community nurse or the health centre?

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR

This section is divided into the following subsections:

Introduction
Step 1: Setting up for an injection
Step 2: Preparing the injection syringe
Step 3: Choosing and preparing an injection site
Step 4a: Injecting Relistor using a pack containing injection syringe with retractable injection needle
Step 4b: Injecting Relistor using a standard injection syringe and injection needle
Step 5 Disposing of supplies

Introduction

The following instructions explain how to inject Relistor. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor, nurse or pharmacist on the techniques of self-administration. Do not attempt to administer an injection until you are sure that you understand how to give the injection. This injection should not be mixed in the same syringe with any other medicine.

You may receive either a pack containing an inner carton with everything needed for the injection, or a single vial only. If you receive only the vial, you will need to obtain alcohol swabs and an injection syringe.

Step 1: Setting up for an injection

1. Select a flat, clean, well-lit working surface where you can lay out the contents of your Relistor carton. Make sure you have set aside a proper amount of time to complete the injection.

2. Wash your hands thoroughly with soap and warm water.

3. Assemble the supplies you will need for your injection. These include the Relistor vial, a 1 mL injection syringe (with or without retractable needle), 2 alcohol swabs, and a cotton ball or gauze.

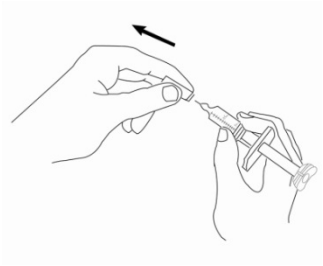
4. Make sure the solution in the vial is clear and colourless to pale yellow, and does not contain flakes or particles. If it is not, do not use the solution. Contact your pharmacist, nurse or doctor for assistance.

Step 2: Preparing the injection syringe

1. Remove the protective plastic cap from the vial.

2. Wipe the vial's rubber stopper with an alcohol swab and place it on your flat work surface. Make sure not to touch the rubber stopper again.

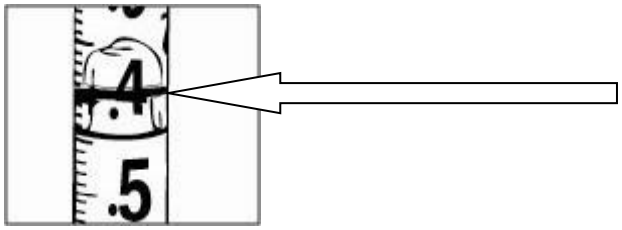
3. Pick up the syringe from your work surface. Hold the barrel of the syringe with one hand and pull the needle cover straight off. Place the needle cover back on the work surface. DO NOT touch the needle or allow it to come into contact with any other surface.



Carefully pull back the plunger on the syringe to either the 0.4 mL mark for 8 mg of Relistor or the 0.6 mL mark for 12 mg Relistor. Your doctor, nurse or pharmacist will have advised you which dose they have prescribed for you and how often you need to take it. For patients receiving supportive care for advanced illness, the usual doses are given in the table below. The dose is normally given every 48 hours (every two days) as an injection under the skin.

Patient weight in kg	Fill syringe to mL level (dose)
Less than 38 kg	0.15 mg/kg
38-61 kg	0.4 mL (8 mg)
62-114 kg	0.6 mL (12 mg)
More than 114 kg	0.15 mg/kg

For patients with long-term pain (except patients receiving supportive care for advanced illness), fill the syringe to the 0.6 mL mark for 12 mg of Relistor.



Carefully pull back the plunger to correct level on syringe (e.g. 0.4 mL if you have been prescribed 8 mg)

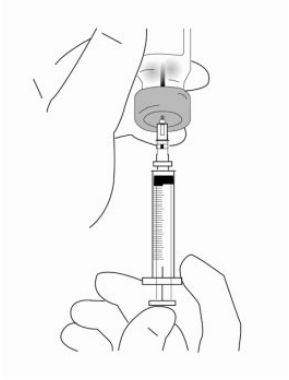
4. Insert the needle straight down into the centre of the vial stopper. Do not insert it at an angle as the needle may bend or break. Hold the vial on the work surface with the other hand so that it can not slip off. You will feel a slight resistance as the needle passes through the stopper. Look for the needle tip inside the vial.

5. In order to get the air out of the syringe, gently push the plunger down to inject the air into the vial.

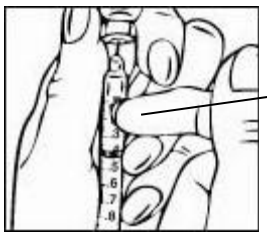
6. If you are using the supplied injection syringe with retractable injection needle, DO NOT PUSH THE PLUNGER DOWN COMPLETELY. Make sure you stop pushing the plunger when you feel resistance. If you push the plunger completely, you will hear a 'click' sound. This will mean that the safety mechanism has been activated, and the needle will disappear

into the syringe. If this happens, discard the product and start again using another vial and syringe.

With the needle still in the vial, turn the vial upside-down. Hold the syringe at eye level so that you can see the dosing marks and make sure the tip of the needle is in the fluid all of the time. Slowly pull the plunger down to the 0.4 mL or 0.6 mL mark on the syringe or as advised, depending on the dose prescribed by your doctor, nurse or pharmacist. You may see some fluid or bubbles inside the vial when the syringe is properly filled. This is normal.

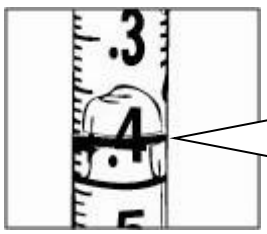


7. With the needle still inserted in the upside down vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe; be sure that you still hold onto the vial and syringe. Slowly push the plunger up until all air bubbles are removed. If you push solution back into the vial, slowly pull back the plunger to draw the correct amount of solution back into the syringe. Due to the safety design of the syringe, a small air bubble may be resistant to removal. There is no need to worry about this as it will not affect the accuracy of the dose or pose any risk to your health.



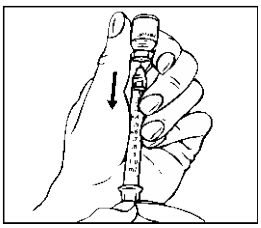
Tap the upside down syringe and push out any air bubbles with the plunger

8. Always make sure you have the correct dose in the syringe. If unsure, please contact your doctor, nurse or pharmacist.



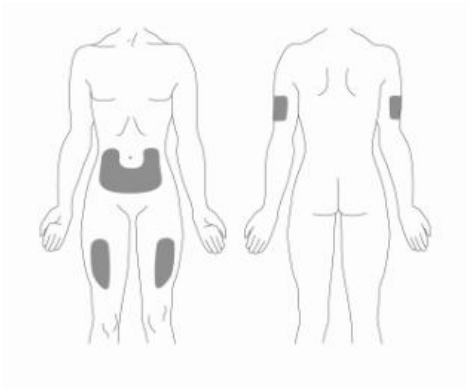
Ensure you have the correct dose level in the syringe (e.g. 0.4 mL if you have been prescribed 8 mg)

9. Remove the syringe and needle from the vial. Keep the needle attached to the syringe. Do not touch the needle or allow the needle to touch any surface. Once you have drawn the medicine into the syringe, it must be used within 24 hours because Relistor is affected by light and may not work properly if it is left in the syringe for longer than 24 hours.



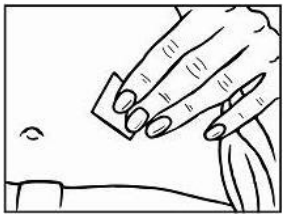
Step 3: Choosing and preparing an injection site

1. The three areas of the body recommended for injection of Relistor are: (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (only if injecting another person).



2. It is recommended to move to a different site each time an injection is given. Avoid repeated injections at the exact same spot previously used. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

3. To prepare the area of skin where Relistor is to be injected, wipe the injection site with an alcohol swab. DO NOT TOUCH THIS AREA AGAIN BEFORE GIVING THE INJECTION. Allow the injection site to air-dry before injecting.

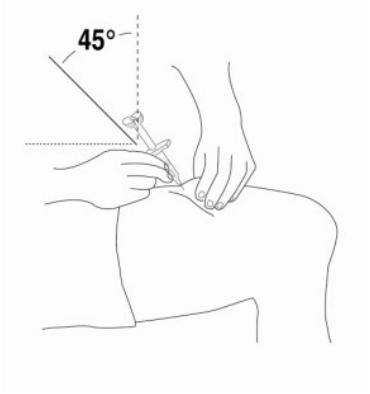


Step 4a: Injecting Relistor using a pack containing injection syringe with retractable injection needle

1. Holding the filled syringe with the needle pointing up, recheck the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

2. Hold the syringe in one hand like a pencil. Use the other hand to gently pinch the cleaned area of skin and hold it firmly.

3. Push the full length of the needle into the skin at a slight angle (45 degrees) with a quick, short motion.



4. After the needle is inserted, let go of the skin and slowly push the plunger all the way down until the syringe is empty and you hear a click to inject Relistor.

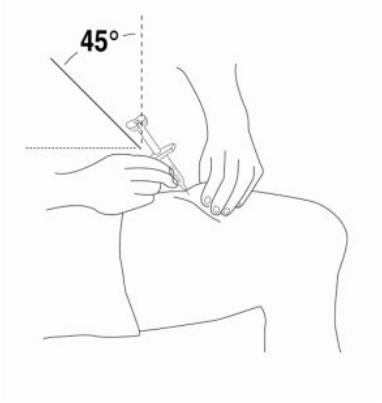
5. When you hear a click sound that means the entire contents were injected. The needle will automatically retract from the skin and be capped. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection site with a plaster.

Step 4b: Injecting Relistor using a standard injection syringe and injection needle

1. Holding the filled syringe with the needle pointing up, recheck the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

2. Hold the syringe in one hand like a pencil. Use the other hand to gently pinch the cleaned area of skin and hold it firmly.

3. Push the full length of the needle into the skin at a slight angle (45 degrees) with a quick, short motion.



4. After the needle is inserted, let go of the skin and slowly push the plunger all the way down to inject Relistor.

5. When the syringe is empty, quickly pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a

cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection site with a plaster.

Step 5: Disposing of supplies

The capped syringe or syringe and needle should NEVER be reused. NEVER recap the needle. Dispose of the capped syringe or needle and syringe in a closable puncture-resistant container as instructed by your doctor, nurse or pharmacist.

Package leaflet: Information for the user

Relistor 8 mg solution for injection in pre-filled syringe
Relistor 12 mg solution for injection in pre-filled syringe
Methylnaltrexone bromide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Relistor is and what it is used for

Relistor contains an active substance called methylnaltrexone bromide which acts by blocking the side effects of opioid pain medicines that affect the bowel.

It treats constipation that is caused by medicines for moderate to severe pain called opioids (for example morphine or codeine). It is used for patients when other medicines for constipation, called laxatives, have not worked well enough. Opioids are prescribed by your doctor. Your doctor will tell you whether you should stop or continue taking your usual laxatives when you start using this medicine.

This medicine is for use in adults (aged 18 and over).

2. What you need to know before you use Relistor

Do not use Relistor
- if you are allergic to methylnaltrexone bromide or any of the other ingredients of this medicine (listed in section 6).
- If you or your doctor know that your bowels were or are obstructed or your bowels are in a state where there is an immediate need for surgical intervention (which has to be diagnosed by your doctor).

Warnings and precautions
Talk to your doctor or pharmacist before using Relistor
- If you have severe stomach symptoms which continue or get worse, contact your doctor immediately because these could be symptoms of a hole developing in the bowel wall (intestinal perforation). See section 4.
- If you have Crohn´s disease or gastrointestinal ulcers
- If you feel sick, vomit, shiver, sweat, have belly pain and/or feel a fast heart beat shortly after taking Relistor talk to your doctor

- If you have severe liver or kidney disease.
- If you develop severe or persistent diarrhoea (passing of frequent watery stools), discontinue therapy and contact your doctor immediately.
- It is important to be near a toilet with assistance available if necessary, since bowel movement may happen within 30 minutes after injection of the medicine.
- Please talk to your doctor if you experience stomach ache which continues, nausea, (feeling sick) or vomiting (being sick) that is new or becomes worse.
- Please also talk to your doctor if you have a colostomy, a tube in your abdomen (peritoneal catheter), or suffer from diverticular disease or faecal impaction as this medicine should be used carefully in these circumstances.
- If you are receiving supportive care for your advanced illness, this medicine will only be used for a limited period of time which will usually be less than 4 months..
- This medicine should not be used for treatment of patients with constipation which is not related to opioid use. If you have suffered from constipation before you had to take opioids (for pain), please talk to your doctor.

Children and adolescents
Do not give this medicine to children and adolescents under the age of 18 because the potential risks and benefits are not known.

Other medicines and Relistor
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Your doctor may allow you to take other medicines, including those used for constipation.

Pregnancy and breast-feeding
The effects of methylnaltrexone bromide in pregnant women are not known. Your doctor will decide if you can use Relistor if you are pregnant.

Women using this medicine should not breast-feed, since it is not known if methylnaltrexone bromide passes into human breast milk.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Dizziness is a common side effect of this medicine. This may have an effect on your ability to drive and use machines.

Important information about some of the ingredietns of Relistor
This medicine contains less than 1 mmol sodium (23 mg) per dose i.e., essentially “sodium free.”

3. How to use Relistor

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for patients with long-term pain (except patients receiving supportive care for advanced illness) is 12 mg methylnalrexone bromide (0.6 mL of solution) given as an injection under the skin , as needed, but at least given 4 times a week and up to once a day (7 times a week).

The 8 mg pre-filled syringe will only be used to treat these patients if the dose needs to be decreased because of another medical problem.

The recommended dose for patients receiving supportive care in advanced illness is 8 mg methylnaltrexone bromide (0.4 mL of solution) for patients weighing 38-61 kg or 12 mg (0.6 mL of solution) for patients weighing 62-114 kg. The dose is given every 48 hours (every two days) as an injection under the skin.

Your doctor will determine your dose.

If you weigh less than 38 kg or more than 114 kg you should use Relistor vials because the correct dose cannot be accurately delivered with these pre-filled syringes.

This medicine is given by an injection under the skin (by subcutaneous injection) in either (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (if not self-injecting). (See INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR at the end of this leaflet.)

You may have a bowel movement within a few minutes to a few hours of the injection; therefore, it is recommended to have a toilet facility or bedpan near you.

If you use more Relistor than you should
If you have used more of this medicine than you should (either by injecting too much on a single occasion or by using more than one injection in 24 hours), you may feel dizzy when standing up, so talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Relistor
If you forget a dose, talk to your doctor or pharmacist as soon as possible. Do not take a double dose to make up for a forgotten dose.

If you stop using Relistor
You should talk to a doctor or pharmacist if you want to stop using this medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Cases of a hole developing in the bowel wall (gastrointestinal perforation) have been reported in patients using Relistor. How often this happens is not known from the data that is available. If you get a stomach ache that is either severe or will not go away, stop taking this medicine and call your doctor straight away.

The following side effects are very common and may affect more than 1 in 10 people. If you experience any of these side effects, which are either severe or will not go away, you should talk to your doctor:

- Abdominal pain (belly ache)
- Nausea (feeling sick)
- Diarrhoea (passing of frequent watery stools)
- Flatulence (passing wind)

Other common side effects that may affect up to 1 in 10 people are:

- Dizziness (light-headed)
- Opioid-withdrawal-like symptoms (any of the following: feeling cold, shivering, runny nose, sweating, hair standing on end, blushing, fast heart beat)
- Reaction at the site of injection (e.g., stinging, burning, pain, redness, oedema)
- Vomiting

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Relistor

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, tray lid and syringe label after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Only use this medicine if the solution is clear, colourless to pale yellow, and does not contain flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to thow away medicines that you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Relistor contains
- The active substance is methylnaltrexone bromide. Each syringe of 0.4 mL contains 8 mg methylnaltrexone bromide. Each syringe of 0.6 mL contains 12 mg methylnaltrexone bromide. One mL of solution contains 20 mg methylnaltrexone bromide.
- The other ingredients are sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH) and sodium hydroxide (to adjust pH).

What Relistor looks like and contents of the pack

Relistor is a solution for injection. It is clear, colourless to pale yellow, and does not contain flakes or particles.

The following packs are available:

Pack containing 4, 7, 8 or 10 pre-filled syringes with a needle shield.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

Manufacturer

Przedsiębiorstwo Farmaceutyczne Jelfa SA
ul. Wincentego Pola 21
58-500 Jelenia Góra,
Poland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

PATIENT CHECKLIST

This section contains important questions that you will need to answer before you take Relistor, and during treatment with Relistor.

If you answer No to any of the following questions during the course of treatment with your medicine please contact your doctor, nurse or pharmacist.

1. Are you receiving opioid therapy (for example morphine or codeine) for your illness?
2. Has it been 48 hours or longer since your last bowel movement?
3. Are you familiar with the technique of self injection or have you discussed this with your doctor (or nurse or pharmacist)?
4. Are you mobile enough to reach the toilet, or do you have a caregiver looking after you who can help?
5. Do you have a contact number for your community nurse or the health centre?

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR

This section is divided into the following subsections:

Introduction
Step 1: Preparing for an injection
Step 2: Choosing and preparing an injection site
Step 3: Injecting Relistor pre-filled syringe
Step 4: Disposing of supplies

Introduction

The following instructions explain how to prepare and give an injection of Relistor when using a pre-filled syringe. Please read and follow them step by step. You will be instructed by your doctor, nurse or pharmacist on the techniques of self-injection. Do not attempt to administer an injection until you are sure that you understand how to prepare and give an injection.

Important notes:

- **Do not use a Relistor pre-filled syringe more than one time, even if there is medicine in the syringe.**
- **Safely throw away the Relistor pre-filled syringe after use (Step 4).**
- **To avoid needle-stick injuries, do not recap used needles.**

Gather the supplies you will need for your injection:

1. Relistor pre-filled syringe
2. Alcohol swab
3. Cotton ball or gauze
4. Adhesive plaster

Step 1: Preparing for an injection

1. Select a flat, clean, well-lit working surface where you can lay out the contents of your Relistor carton. Make sure you have set aside a proper amount of time to complete the injection.

2. Wash your hands thoroughly with soap and warm water.

3. Look at the pre-filled syringe. Make sure that the dose prescribed by your doctor matches the dose on the pre-filled syringe label.

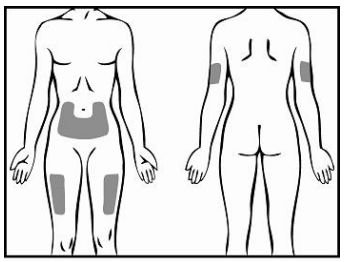
4. Make sure the liquid in the pre-filled syringe is clear and colourless to pale yellow, and does not have any particles in it. If not, do not use the pre-filled syringe and call your nurse, doctor or pharmacist.

5. Firmly hold the barrel of the pre-filled syringe and pull the needle cap straight off.

Do not touch the needle or allow it to touch any surface.

Step 2: Choosing and preparing an injection site

1. The three areas of the body recommended for injection of Relistor are: (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (only if injecting another person).



2. It is recommended to move to a different site each time an injection is given. Avoid repeated injections at the exact same spot previously used. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

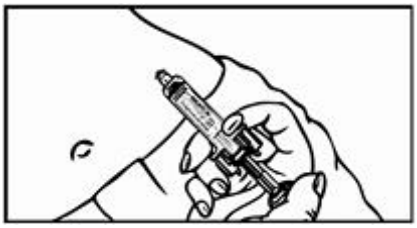
3. Clean the injection site with an alcohol swab and let it dry. Do not touch this area again before giving the injection.

Step 3: Injecting Relistor pre-filled syringe

1. Hold the syringe in one hand like a pencil. Use the other hand to gently pinch the cleaned area of skin and hold it firmly.

2. Push the full length of the needle into the skin at a slight angle (45 degrees) with a quick, short motion.

3. After the needle is inserted, let go of the skin and slowly push the plunger all the way down until the pre-filled syringe is empty.



4. Quickly pull the needle out of the skin, being careful to keep it at the same angle as it was inserted. Release your thumb from the plunger to allow the protective sleeve to cover the needle. There may be a little bleeding at the injection site.

5. You can press a cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection site with a plaster.

Step 4: Disposing of supplies

The pre-filled syringe should NEVER be reused. NEVER recap the needle. Dispose of the pre-filled syringe as instructed by your doctor, nurse or pharmacist.

Place used pre-filled syringe in a closable, puncture-resistant container. You may use a sharps container (such as a yellow biohazard container). Ask your doctor, nurse or pharmacist for instructions on the right way to throw away (dispose of) the container. There may be local laws about how you should throw away used needles and syringes.