

New Zealand Data Sheet

1. PRODUCT NAME

RELISTOR® 12 mg/0.6 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains methylnaltrexone bromide 12 mg/0.6 mL.

One mL of solution contains 20 mg of methylnaltrexone bromide.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Methylnaltrexone bromide is a sterile, clear and colourless to pale yellow aqueous solution. Chemically it is (R)-N-(cyclopropylmethyl) noroxymorphone methobromide. Its molecular formula is $C_{21}H_{26}NO_4Br$ and its molecular weight 436.36.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient.

4.2 Dose and method of administration

Usual dosage

FOR SUBCUTANEOUS INJECTION ONLY

Contains no antimicrobial agent. RELISTOR is for single use in one patient only. Discard any residue.

RELISTOR should be injected in the upper arm, abdomen or thigh. 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.

RELISTOR is administered as a single dose on alternate days. Doses may also be given with longer intervals, as needed. If there has been no bowel movement within 24 hours of the last dose, an additional dose may be given. In clinical trials, RELISTOR was administered concomitantly with a laxative regimen.

RELISTOR can be injected without regard to food. The recommended dose of RELISTOR is detailed in the table below.

| Patient Weight (kg) | Injection Volume | Dose |
|-------------------------------|---|------------|
| 38 to less than 62 | 0.4 mL | 8 mg |
| 62 to 114 | 0.6 mL | 12 mg |
| Less than 38 or more than 114 | Patient weight (kg) x 0.0075; rounded to nearest 0.1 mL | 0.15 mg/kg |

Use in patients with renal impairment

In patients with severe renal impairment (creatinine clearance less than 30 mL/min) reduce the dose of RELISTOR by one-half. No dose adjustment is required in patients with mild or moderate renal impairment. There are no data available from patients with end-stage renal impairment on dialysis, and therefore, is not recommended in these patients.

Use in patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. There are no data available from patients with severe hepatic impairment (Child-Pugh Class C), and therefore, is not recommended in these patients.

Use in children

Safety and efficacy of RELISTOR have not been established in paediatric patients.

Use in elderly patients

No dose adjustment is recommended based on age.

4.3 Contraindications

RELISTOR is contraindicated in patients with:

- a known hypersensitivity to the drug or any of its components
- known or suspected mechanical gastrointestinal obstruction or acute surgical abdomen

4.4 Special warnings and precautions for use

RELISTOR has been studied in a small population of patients who were receiving palliative care and who had insufficient response to laxative therapy. Use of RELISTOR beyond 4 months has not been studied. Safety and efficacy with longer term use and in other patient groups have not been established.

Use with caution in the following circumstances

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

Cases of gastrointestinal tract perforations have been reported in association with use of methylalnaltrexone bromide in patients with advanced illness and conditions that may be associated with localised or diffuse reduction of structural integrity in the wall of the gastrointestinal tract [(e.g. cancer, peptic ulcer, pseudo- obstruction and concomitant medications known to cause gastrointestinal tract perforations e.g. bevacizumab, non-steroidal anti inflammatory drugs (NSAIDs) and steroids)]. Perforations have involved varying regions of the gastrointestinal tract (e.g. stomach, duodenum, colon).

Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. Advise patients to discontinue therapy with RELISTOR and promptly notify their physician if they develop severe, persistent, and/or worsening abdominal symptoms.

Patients with hepatic or renal impairment

RELISTOR is not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis.

Patients with other conditions

Use of methylnaltrexone bromide in patients with colostomy, peritoneal catheter, active diverticular disease or faecal impaction has not been studied. Therefore, RELISTOR should only be administered with caution in these patients. RELISTOR should not be used in patients with known or suspected mechanical bowel obstruction.

RELISTOR is not recommended for use in post-operative ileus, including patients who have undergone gastrointestinal resection.

Abdominal cramping or abdominal pain are common following treatment with RELISTOR. Patients given RELISTOR who develop severe or persistent abdominal pain that is not relieved by laxation should discontinue treatment and be evaluated by their physician.

Paediatric use

Safety and efficacy of RELISTOR have not been established in paediatric patients

Use in the elderly

In the phase 2 and 3 double-blind studies, a total of 77 patients aged 65-74 years (54 methylnaltrexone, 23 placebo) and a total of 100 patients aged 75 years or older (61 methylnaltrexone, 39 placebo) were enrolled. There was no difference in the efficacy or safety profile of these elderly patients when compared to younger patients. Therefore, no dose adjustment is recommended based on age.

Effect on cardiac repolarization

In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylnaltrexone (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).

4.5 Interactions with other medicines and other forms of interaction

Drugs Metabolised by Cytochrome P450 Isozymes

Methylnaltrexone does not affect the pharmacokinetics of drugs metabolized by cytochrome P450 (CYP) isozymes. Methylnaltrexone is minimally metabolised by CYP isozymes. In vitro drug metabolism studies suggest that methylnaltrexone does not inhibit the activity of CYP1A2, 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 0.30 mg/kg of methylnaltrexone did not significantly affect the metabolism

of dextromethorphan, a CYP2D6 substrate.

Abuse and dependence

RELISTOR is a peripherally acting mu-opioid receptor antagonist with no known risk of abuse and/or dependence.

Onset of action

Data from clinical trials demonstrated that RELISTOR may induce rapid onset (within 30 minutes) of a bowel movement (see section 5.1 Pharmacodynamic properties, Clinical trials). Patients should therefore be advised to remain close to toileting facilities after each dose.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

There are no adequate and well-controlled studies in pregnant women using methylnaltrexone bromide. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. The potential for teratogenic effects of RELISTOR on the human foetus is unknown. Reproduction studies have been performed in pregnant rats and rabbits. There were no effects on foetal development at intravenous doses of up to 25 mg/kg/day in the rat or up to 16 mg/kg/day in the rabbit, which resulted in respective drug exposures [AUC] of 165 and 82 times that expected in humans treated with the normal therapeutic dose.

Labour and delivery

Methylnaltrexone at subcutaneous doses of up to 25 mg/kg/day had no effect on labour, delivery and offspring development in rats. This dose resulted in a drug exposure that was 36 times that expected in humans treated with the normal therapeutic dose. Reduced postnatal weight gain of offspring and slightly delayed female sexual maturation were observed at a higher dose (100 mg/kg/day).

Breast-feeding

It is not known whether RELISTOR is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if RELISTOR is administered to a nursing woman. Methylnaltrexone and/or its metabolites are excreted in the milk of lactating rats.

Fertility

Subcutaneous treatment of rats with methylnaltrexone at a dose (25 mg/kg/day) resulting in estimated exposures (based on AUC) that were 36 times clinical exposure had no effect on fertility. Slightly decreased fertility was observed with a subcutaneous dose of 150 mg/kg/day.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive have been performed. However, as a pure peripherally restricted opioid antagonist, the likelihood that methylnaltrexone will affect driving is low. Dizziness may occur, and this may have an effect on driving.

4.8 Undesirable effects

In the clinical development program 286 patients have received at least one dose of RELISTOR and 23 patients have received RELISTOR intermittently for 3 to 4 months.

| Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR* | | |
|---|-----------------------------|----------------------------|
| Adverse Reaction | RELISTOR n = 165 | Placebo n = 123 |
| Abdominal Pain | 47 (28.5%) | 12 (9.8%) |
| Flatulence | 22 (13.3%) | 7 (5.7%) |
| Nausea | 19 (11.5%) | 6 (4.9%) |
| Dizziness | 12 (7.3%) | 3 (2.4%) |
| Diarrhoea | 9 (5.5%) | 3 (2.4%) |

* Doses: 0.075, 0.15 and 0.30 mg/kg/dose

Clinical trial experience

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients receiving palliative care: Study 301 included a single-dose, double-blind, placebo-controlled period, whereas Study 302 included a 14-day multiple-dose, double-blind, placebo-controlled period. In both studies, patients had advanced illness 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. Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either < 3 bowel movements in the preceding week or no bowel movement for 2 days). Both the methylnaltrexone and placebo patients were on a stable laxative regimen for at least 3 days prior to study entry and continued on their regimen throughout the study.

Post-Marketing Experience

Expected frequency of adverse reactions is presented in CIOMS frequency categories:

| | |
|--------------|------------------|
| Very common: | ≥10% |
| Common: | ≥1% and <10% |
| Uncommon: | ≥0.1% and <1% |
| Rare: | ≥0.01% and <0.1% |

Skin and subcutaneous tissue disorders

Common: Hyperhidrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone overdose were reported. In a study of healthy volunteers (n = 41), a single dose of 0.50 mg/kg administered as a subcutaneous injection was well tolerated. A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

Management

In the event of an overdose, signs and symptoms of orthostatic hypotension should be monitored and treatment should be initiated, as appropriate.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

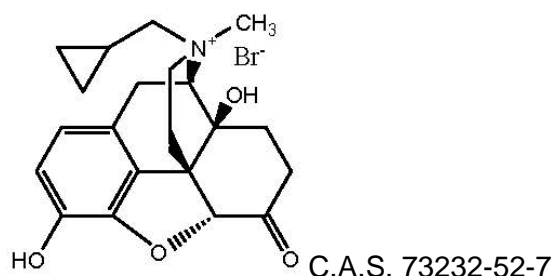
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Chemical structure

Methylnaltrexone bromide



Mechanism of action

Methylnaltrexone is a competitive antagonist of opioid receptor binding with an 8-fold selectivity for the mu-opioid receptor over the kappa-receptor. It does not interact significantly with the delta-opioid receptor. As a quaternary amine, the ability of methylnaltrexone to cross the blood brain barrier is restricted. This allows methylnaltrexone 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 trials

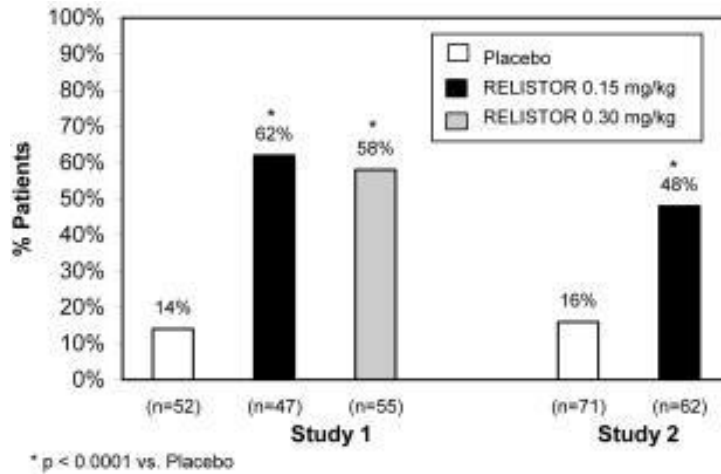
The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in patients receiving palliative care was demonstrated in two randomised, double-blind, placebo-controlled

studies. In these studies, the median age was 68 years (range 21-100); 51% were females. In both studies, patients had advanced illness, 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 and had a life expectancy of less than 6 months. Prior to screening, patients had been receiving palliative opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either < 3 bowel movements in the preceding week or no bowel movement for > 2 days). Patients were on a stable opioid regimen \geq 3 days prior to randomisation (not including PRN or rescue pain medication) and received their opioid medication during the study as clinically needed. Patients maintained their regular laxative regimen for at least 3 days prior to study entry, and throughout the study. Rescue laxatives were prohibited from 4 hours before to 4 hours after taking an injection of study medication. Twenty-three patients received RELISTOR intermittently for a period of 3-4 months. No longer term efficacy information is available.

Study 301 compared a single, double-blind, subcutaneous dose of RELISTOR 0.15 mg/kg, or RELISTOR 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label, 4-week dosing period, where RELISTOR could be used as needed, no more frequently than 1 dose in a 24-hour period. Throughout both study periods, patients maintained their regular laxative regimen. A total of 154 patients (47 RELISTOR 0.15 mg/kg, 55 RELISTOR 0.3 mg/kg, 52 placebo) were enrolled and 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 medication. RELISTOR-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 did placebo-treated patients (14%); $p < 0.0001$ for each dose versus placebo (Figure 1).

Study 302 compared double-blind, subcutaneous doses of RELISTOR given every other day for 2 weeks versus placebo. Patients received opioid medication \geq 2 weeks prior to receiving study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg RELISTOR or placebo. In the second week, the 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 RELISTOR, 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 medication and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of study medication. RELISTOR-treated patients had a higher rate of laxation within 4 hours of the first dose (48%) than placebo-treated patients (16%); $p < 0.0001$ (Figure 1). RELISTOR-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%); $p < 0.0001$.

Figure 1. Laxation Response Within 4 Hours of the First Dose



In both studies, approximately half of those patients who responded to RELISTOR within 4 hours had a laxation within 30 minutes (Figure 2a, b). In addition, there was no evidence to suggest differential effects of age or gender on safety or efficacy. No meaningful subgroup analysis could be conducted on race because the study population was predominantly Caucasian (88%).

Figure 2a: Time of Onset of Laxation within 4 Hours of Dose 1 (Study 301)

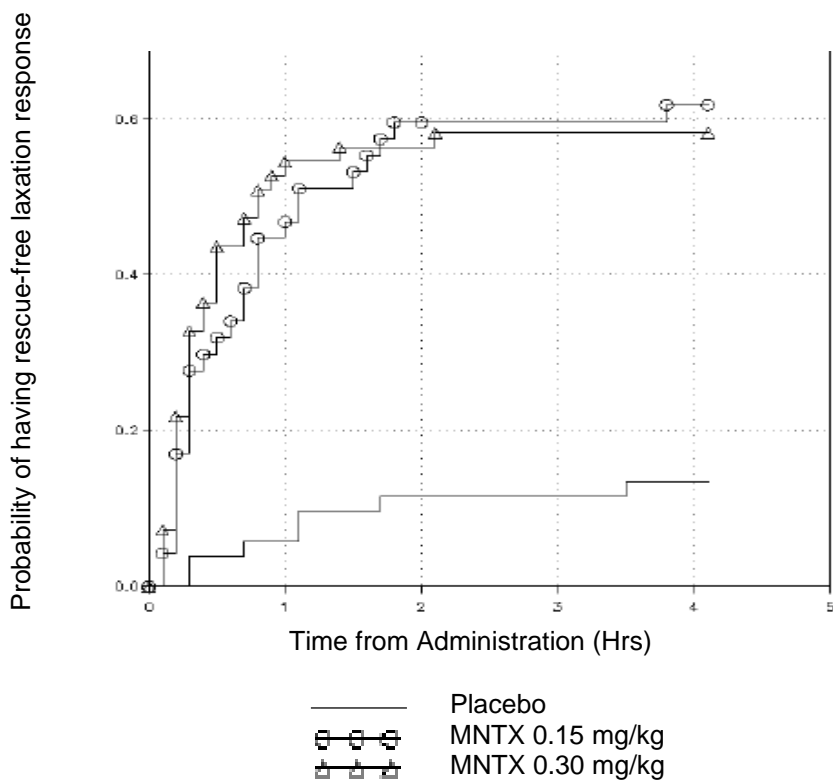
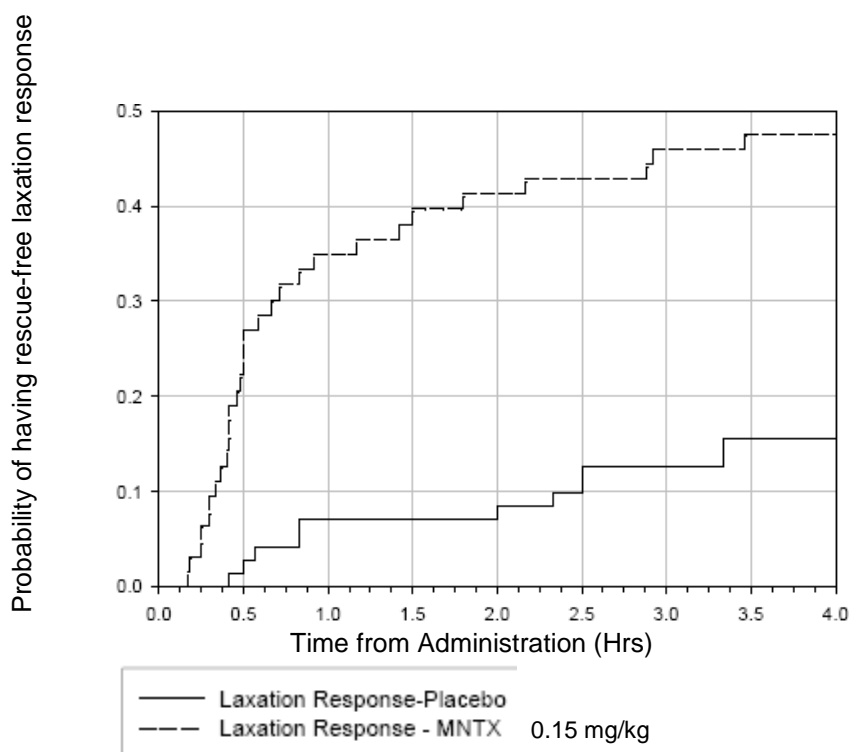


Figure 2b: Time of Onset of Laxation within 4 Hours of Dose 1 (Study 302)



Durability of response

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

During the open-label treatment periods in studies 301, 301EXT and 302EXT, the laxation response rates observed were comparable to those seen for active methylnaltrexone (MNTX) during double-blind treatment. Patients used methylnaltrexone (MNTX) as needed with a median of 3.2 days between doses. Laxation rates were generally stable over the course of 3 to 4 months of open label treatment.

Opioid use and pain scores

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

5.2 Pharmacokinetic properties

Absorption

Methylnaltrexone is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours following subcutaneous administration. Peak plasma concentration and area under the plasma concentration-time curve (AUC) increase in a dose proportional manner. The mean C_{max} (±SD) values were 117 ± 33 ng/mL, 234 ± 65 ng/mL and 392 ± 148 ng/mL at 0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg, respectively. The mean AUC values were 180 ± 37 ng•h/mL, 376 ± 73 ng•h/mL, and 593 ± 111 ng•h/mL at 0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg,

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

Distribution

Methylnaltrexone undergoes moderate tissue distribution. The steady-state volume of distribution (V_{ss}) is approximately 1.1 L/kg. Methylnaltrexone is minimally bound to human plasma proteins *in vitro* (about 11.0% at a concentration close to the plasma C_{max}) as determined by equilibrium dialysis.

Metabolism

Methylnaltrexone is minimally metabolised in humans. Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulfate appears to be the primary pathway of metabolism. Each of the methyl-6-naltrexol isomers has somewhat less antagonist activity than the parent compound and a low exposure in plasma of approximately 8% of the drug-related materials. Methylnaltrexone sulfate is an inactive metabolite and present in plasma at a level of approximately 25% of drug-related materials. N-demethylation of methylnaltrexone to produce naltrexone is not significant (0.06% of the administered dose).

Elimination

Methylnaltrexone is eliminated primarily as the unchanged drug. Approximately half of the dose is excreted in the urine and somewhat less in faeces. The terminal disposition half-life ($t_{1/2}$) is approximately 8 hours.

Elderly

In the phase 2 and 3 double-blind studies, a total of 77 patients aged 65-74 years (54 methylnaltrexone, 23 placebo) and a total of 100 patients aged 75 years or older (61 methylnaltrexone, 39 placebo) were enrolled. There was no difference in the efficacy or safety profile of these elderly patients when compared to younger patients. Therefore, no dose adjustment is recommended based on age.

Children

The pharmacokinetics of methylnaltrexone have not been studied in children.

Patients with renal impairment

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

Patients with hepatic impairment

The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone 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. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone has not been studied.

Effect of body weight on exposure to methylnaltrexone

An integrated analysis of pharmacokinetic data from 137 healthy subjects who received RELISTOR subcutaneously with the mg/kg dosing adjustment used in studies 301 and 302 indicated that methylnaltrexone exposure (AUC) per unit dose (mg/kg) increased as body weight increased. In addition, the analysis showed that equivalent methylnaltrexone exposure to that at 0.15 mg/kg can be achieved with a two weight-band-based dosing adjustment of an 8 mg dose for body weight 38 to less than 62 kg or a 12 mg dose for body weight 62 to 114 kg.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenesis studies have not been conducted with methylnaltrexone.

Genotoxicity

Methylnaltrexone was not genotoxic in *in vitro* tests for bacterial gene mutation forward mutation in mammalian cells or chromosome aberrations in Chinese hamster ovary cells and human lymphocytes. There was no evidence of genotoxicity in *in vivo* mouse micronucleus tests for clastogenicity at exposures of more than 200 times clinical exposure at the maximal recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients are 3.9 mg sodium chloride, 0.24 mg sodium calcium edetate, and 0.18 mg glycine hydrochloride per 0.6 mL injection. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

Use as soon as possible after withdrawal into the syringe. Once drawn into the syringe, if immediate administration is not possible, store at room temperature for not more than 6 hours.

6.4 Special precautions for storage

RELISTOR injection should be stored below 30°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

The following packs are available:

- A single 3 mL vial containing 12 mg of methylnaltrexone bromide.
- A convenience pack containing 7 cartons. Each carton contains one vial, one 1 mL syringe and two alcohol swabs.

Each single-use vial of RELISTOR injection contains 12 mg of methylnaltrexone bromide in 0.6 mL of water, with a concentration of 20 mg/mL of methylnaltrexone bromide.

RELISTOR injection is provided in a clear, Type I, flint glass, single use vial with a grey butyl rubber stopper and aluminium overseal with flip-off-cap. RELISTOR is a sterile, clear and colourless to pale yellow aqueous solution.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

5 May 2016

10. DATE OF REVISION OF THE TEXT

25 November 2020

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|-----------------|----------------------------|
| 8 | Update Sponsor details |

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