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 $C_{\text{max}}$, 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 ($\geq$1/10); common ($\geq$1/100 to $<$1/10); uncommon ($\geq$1/1,000 to $<$1/100); rare ($\geq$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 methylaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylaltrexone 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 methylaltrexone 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 methylaltrexone bromide 12 mg once daily and methylaltrexone 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 methylaltrexone bromide was to be used as needed, but no more frequently than once daily. A total of 460 patients (methylaltrexone bromide 12 mg once daily, n=150, methylaltrexone 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 bromide 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 bromide 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. Methylaltrexone 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 methylaltrexone bromide given every other day for 2 weeks versus placebo. During the first week (days 1, 3, 5, 7), patients received either methylaltrexone 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 methylaltrexone 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. Methylaltrexone 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. Methylaltrexone 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 methylaltrexone 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 methylaltrexone 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 methylaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either methylaltrexone bromide-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylaltrexone bromide or placebo-treated patients.

**Effect on cardiac repolarisation**

In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylaltrexone 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**

Methylaltrexone 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 Cmax 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). Cmax 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 Cmax 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