HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Warnings and Precautions, Intestinal Perforation (*5.2*) [05/2010]

Dosage and Administration, Dosing (*2.2*) [09/2010]

INDICATIONS AND USAGE

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. Use of RELISTOR beyond four months has not been studied. (*1*)

DOSAGE AND ADMINISTRATION

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period. (*2.2*)

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weights fall outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume. (*2.2*)

Patient Weight		**Injection Volume**	**Dose**
Pounds	Kilograms		
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

* The injection volume for these patients should be calculated using one of the following (*2.2*):

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

Only patients requiring an 8 mg or 12 mg dose should be prescribed pre-filled syringes (*2.2, 3*).

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reductions of RELISTOR by one half is recommended. (*8.6*)

DOSAGE FORMS AND STRENGTHS

RELISTOR is available in the following dosage forms:

- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection.
- Single-use pre-filled syringe containing 8 mg/0.4 mL solution for subcutaneous injection.
- Single-use pre-filled syringe containing 12 mg/0.6 mL solution for subcutaneous injection.

CONTRAINDICATIONS

- RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (*4*)

WARNINGS AND PRECAUTIONS

- If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician. (*5.1*)
- Rare cases of gastrointestinal (GI) perforation have been reported in advanced illness patients. Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. (*5.2*)

ADVERSE REACTIONS

The most common (> 5%) adverse reactions reported with RELISTOR are abdominal pain, flatulence, nausea, dizziness, diarrhea and hyperhidrosis. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

In an *in vitro* study, methylnaltrexone bromide was a weak inhibitor of cytochrome P450 (CYP) isozyme CYP2D6 activity, but in an *in vivo* study it did not significantly affect the metabolism of the CYP2D6 substrate, dextromethorphan (*7.1*)

USE IN SPECIFIC POPULATIONS

Pediatric Use: Safety and efficacy of RELISTOR have not been established in pediatric patients. (*8.4*)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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. Use of RELISTOR beyond four months has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR SUBCUTANEOUS INJECTION ONLY

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

2.2 Dosing

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period [*see Clinical Studies (14)*].

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume. The pre-filled syringe is designed to deliver a fixed dose; therefore, patients requiring dosing calculated on a mg/kg basis should not be prescribed pre-filled syringes.

Patient Weight		**Injection Volume**	**Dose**
Pounds	Kilograms		
Less than 84	Less than 38	**See below***	0.15 mg/kg
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg
More than 251	More than 114	**See below***	0.15 mg/kg

*The injection volume for these patients should be calculated using one of the following:

- Multiply the patient weight in pounds by 0.0034 and round up the volume to the nearest 0.1 mL.
- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

Use in Patients with Severe Renal Impairment

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reduction of RELISTOR by one-half is recommended [*see Use in Specific Populations (8.6)*].

The pre-filled syringe is designed to deliver a fixed dose; therefore, patients with severe renal impairment should not be prescribed pre-filled syringes unless their body weight calculated dose is 8 mg or 12 mg.

2.3 Preparation for Injection

RELISTOR is a sterile, clear, and colorless to pale yellow aqueous solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these are present, the vial should not be used.

Preparation of RELISTOR Using the Single-use Vial

Once drawn into the syringe, if immediate administration is not possible, store at ambient room temperature and administer within 24 hours [*see Patient Counseling Information (17)*].

Preparation of RELISTOR Using the Single-use Pre-filled Syringe

Do not remove the pre-filled syringe from the tray until ready to administer.

3 DOSAGE FORMS AND STRENGTHS

RELISTOR is available in the following dosage forms and strengths. Only patients requiring an 8 mg or 12 mg dose should be prescribed pre-filled syringes.

- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection [*see Dosage and Administration (2.2)*].
- Single-use pre-filled syringe containing 8 mg/0.4 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard [*see Dosage and Administration (2.2)*].
- Single-use pre-filled syringe containing 12 mg/0.6 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard [*see Dosage and Administration (2.2)*].

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

5.2 Intestinal Perforation

Rare cases of gastrointestinal (GI) perforation have been reported in advanced illness patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (i.e., cancer, peptic ulcer, Ogilvie's syndrome). Perforations have involved varying regions of the GI 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.

5.3 Peritoneal Catheters

Use of RELISTOR has not been studied in patients with peritoneal catheters.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients with advanced illness receiving palliative care: Study 1 included a single-dose, double-blind, placebo-controlled period, whereas Study 2 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14)*]. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had 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 bromide 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.

The adverse reactions in patients receiving RELISTOR are shown in table below.

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%)
Diarrhea	9 (5.5%)	3 (2.4%)
Hyperhidrosis	11 (6.7%)	8 (6.5%)

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

6.2 Postmarketing Experience

Rare cases of gastrointestinal (GI) perforation have been reported in advanced illness patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (i.e., cancer, peptic ulcer, Ogilvie's syndrome). Perforations have involved varying regions of the GI tract: (e.g., stomach, duodenum, colon). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450 Isozymes

In *in vitro* drug metabolism studies methylnaltrexone bromide did not significantly inhibit the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of CYP2D6. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

7.2 Drugs Renally Excreted

The potential for drug interactions between methylnaltrexone bromide and drugs that are actively secreted by the kidney has not been investigated in humans.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in pregnant rats at intravenous doses up to about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area and in pregnant rabbits at intravenous doses up to about 17 times the recommended maximum human subcutaneous dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, methylnaltrexone bromide should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Effects of RELISTOR on mother, fetus, duration of labor, and delivery are unknown. There were no effects on the mother, labor, delivery, or on offspring survival and growth in rats following subcutaneous injection of methylnaltrexone bromide at dosages up to 25 mg/kg/day.

8.3 Nursing Mothers

Results from an animal study using [^{3}H]-labeled methylnaltrexone bromide indicate that methylnaltrexone bromide is excreted via the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELISTOR is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the phase 2 and 3 double-blind studies, a total of 77 (24%) patients aged 65-74 years (54 methylnaltrexone bromide, 23 placebo) and a total of 100 (31.2%) patients aged 75 years or older (61 methylnaltrexone bromide, 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.

8.6 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose-reduction by one half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

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. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold and resulted in 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.

8.7 Hepatic Impairment

No dose adjustment is required for patients with mild or moderate 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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylnaltrexone bromide is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

RELISTOR is a peripherally-acting mu-opioid receptor antagonist with no known risk of dependency.

10 OVERDOSAGE

10.1 Human Experience

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone bromide 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 IV bolus.

10.2 Management of Overdosage

No specific information is available on the treatment of overdose with RELISTOR. In the event of overdose, employ the usual supportive measures, e.g., clinical monitoring and supportive therapy as dictated by the patient's clinical status. Signs or symptoms of orthostatic hypotension should be monitored, and treatment should be initiated, as appropriate.

11 DESCRIPTION

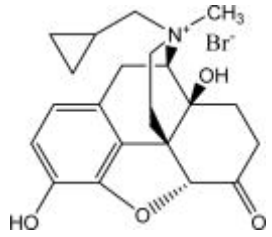
RELISTOR (methylnaltrexone bromide) Subcutaneous Injection, a peripherally-acting mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$, and the molecular weight is 436.36.

Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Each 8 mg/0.4 mL pre-filled syringe (1 mL syringe) contains 8 mg of methylnaltrexone bromide in 0.4 mL of water. The excipients are 2.6 mg sodium chloride USP, 0.16 mg edetate calcium disodium USP, and 0.12 mg glycine hydrochloride.

Each 12 mg/0.6 mL pre-filled syringe (1 mL syringe) contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride.

The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-opioid receptor. 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 receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

12.2 Pharmacodynamics

Use of opioids induces slowing of gastrointestinal motility and transit. Antagonism of gastrointestinal mu-opioid receptors by methylnaltrexone bromide inhibits opioid-induced delay of gastrointestinal transit time in a dose-dependent manner in rats. The effects of methylnaltrexone bromide on central mu-opioid receptors were evaluated in a pharmacodynamic study in which subjects received a dose of remifentanil, sufficient to produce pupiliary constriction, followed by placebo, naloxone, or methylnaltrexone. Following remifentanil

administration, the methylnaltrexone and placebo groups showed no change in pupiliary constriction while the naloxone group showed a marked change over the time interval tested.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours. Across the range of doses evaluated peak plasma concentration and area under the plasma concentration-time curve (AUC) increase in a dose-proportional manner, as shown in the table below.

PHARMACOKINETIC PARAMETERS OF METHYLNALTREXONE BROMIDE FOLLOWING SINGLE SUBCUTANEOUS DOSES

Parameter	**0.15 mg/kg**	**0.30 mg/kg**	**0.50 mg/kg**
C_{max} (ng/mL)[a]	117 (32.7)	239 (62.2)	392 (147.9)
t_{max} (hr)[b]	0.5 (0.25-0.75)	0.5 (0.25-0.75)	0.5 (0.25-0.75)
AUC_{24} (ng·hr/mL)[a]	175 (36.6)	362 (63.8)	582 (111.2)

[a] Expressed as mean (SD).
[b] Expressed as median (range).

Distribution

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

Metabolism

In a mass balance study, approximately 60% of the administered radioactivity recovered with 5 distinct metabolites and none of the detected metabolites was in amounts over 6% of administered radioactivity. Conversion to methyl-6-naltrexol isomers (5% of total) and methylnaltrexone sulfate (1.3% of total) appear to be the primary pathways of metabolism. N-demethylation of methylnaltrexone to produce naltrexone is not significant.

Excretion

Methylnaltrexone bromide is eliminated primarily as the unchanged drug (85% of administered radioactivity). Approximately half of the dose is excreted in the urine and somewhat less in feces. The terminal half-life ($t_{1/2}$) is approximately 8 hours.

12.4 Effect on Cardiac Repolarization

In a randomized, double blind placebo- and (open-label) moxifloxacin-controlled 4-period crossover study, 56 healthy subjects were administered methylnaltrexone bromide 0.3 mg/kg and methylnaltrexone bromide 0.64 mg/kg by IV infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg methylnaltrexone bromide doses, no significant effect on the QTc interval was detected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of methylnaltrexone bromide.

Mutagenesis

Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Impairment of Fertility

Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 81 times the recommended maximum human subcutaneous dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

A single subcutaneous dose of 500 mg/kg of methylnaltrexone bromide was not lethal to rats.

Reproduction studies have been performed in pregnant rats at intravenous doses up to 25 mg/kg/day (about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area) and in pregnant rabbits at intravenous doses up to 16 mg/kg/day (about 17 times the recommended maximum human subcutaneous dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide.

In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone bromide caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 μM concentrations, respectively). Methylnaltrexone bromide had a hERG IC_{50} of > 1000 μM. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 μM) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous (SC)

doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone bromide (up to 100 μM) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 μM) tested was about 186 and 373 times the human C_{max} at SC doses of 0.3 and 0.15 mg/kg, respectively. In anesthetized dogs, methylnaltrexone bromide caused decreases in blood pressure, heart rate, cardiac output, left ventricular pressure, left ventricular end diastolic pressure, and +dP/dt at ≥ 1 mg/kg. In conscious dogs, methylnaltrexone bromide caused a dose-related increase in QTc interval. After a single IV dosage of 20 mg/kg to beagle dogs, predicted C_{max} and AUC values were approximately 482 and 144 times, respectively, the exposure at human SC dose of 0.15 mg/kg and 241 times and 66 times, respectively, the exposure at a human SC dose of 0.3 mg/kg. In conscious guinea pigs, methylnaltrexone caused mild prolongation of QTc (4% over baseline) at 20 mg/kg, IV. A thorough QTc assessment was conducted in humans [*see Pharmacokinetics (12.4)*].

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing occurred at dosages of 3 and 10 mg/kg/day (about 3.2 and 11 times, respectively, the recommended human dose of 0.15 mg/kg based on the body surface area). Similar adverse clinical signs were seen in adult rats at 20 mg/kg/day (about 22 times the recommended human dose of 0.15 mg/kg based on the body surface area). Juvenile rats were found to be more sensitive to the toxicity of RELISTOR when compared to adults. The no observed adverse effect levels (NOAELs) in juvenile and adult rats were 1 and 5 mg/kg/day, respectively (about 1.1 and 5.4 times respectively, the recommended human dose of 0.15 mg/kg based on the body surface area).

In juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks, juvenile dogs had a toxicity profile similar to adult dogs. Following IV administration of methylnaltrexone bromide for 13 weeks, decreased heart rate (13.2 % reduction compared to pre-dose) in juvenile dogs and prolonged QTc interval in juvenile (9.6% compared to control) and adult (up to 15% compared to control) dogs occurred at 20 mg/kg/day (about 72 times the recommended human subcutaneous doses of 0.15 mg/kg based on the body surface area). Clinical signs consistent with effects on the CNS (including tremors and decreased activity) occurred in both juvenile and adult dogs. The NOAELs in juvenile and adult dogs were 5 mg/kg/day (about 18 times the recommended human subcutaneous doses of 0.15 mg/kg based on the body surface area).

14 CLINICAL STUDIES

The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in advanced illness patients receiving palliative care was demonstrated in two randomized, 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 a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had 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 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 ≥ 3 days prior to randomization (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.

Study 1 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 2 compared double-blind, subcutaneous doses of RELISTOR given every other day for 2 weeks versus placebo. Patients received opioid medication ≥ 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 analyzed. 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%); $p < 0.0001$. In both studies, in approximately 30% of patients, laxation was reported within 30 minutes of a dose of RELISTOR.

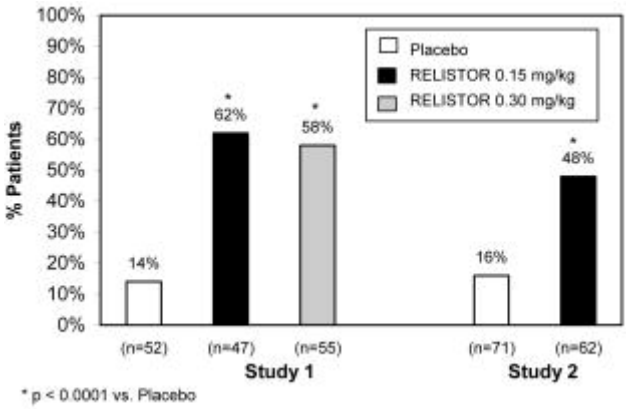


Figure 1. Laxation Response Within 4 Hours of the First Dose

In both studies, there was no evidence of 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%). The rates of discontinuation due to adverse events during the double blind placebo controlled clinical trials (Study 1 and Study 2) were comparable between RELISTOR (1.2%) and placebo (2.4%).

Durability of Response

Durability of response was demonstrated in Study 2, 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 was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 1, and in two open-label extension studies (Study 1EXT and Study 2EXT) in which RELISTOR was given as needed for up to 4 months. During open-label treatment, patients maintained their regular laxative regimen. A total of 136, 21, and 82 patients received at least 1 open-label dose in studies 1, 1EXT, and 2EXT, respectively. Laxation response rates observed during double-blind treatment with RELISTOR were maintained over the course of 3 to 4 months of open-label treatment.

Opioid Use and Pain Scores

There was no 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 RELISTOR-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.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC NUMBER	PACK SIZE	CONTENTS
0008-1218-01	1 vial per carton	one 12 mg/0.6 mL single-use vial
0008-2513-02	7 trays per kit	Each tray contains: one 12 mg/0.6 mL single-use vial, one 1 cc (mL) syringe with retractable (27-gauge x ½-inch) needle (VanishPoint®), two alcohol swabs
0008-1225-10	7 pre-filled syringes per carton	seven 8 mg/0.4 mL single-use pre-filled syringes with needle guard system
0008-1218-10	7 pre-filled syringes per carton	seven 12 mg/0.6 mL single-use pre-filled syringes with needle guard system

16.1 Storage

RELISTOR® should be stored at 20-25ºC (68-77ºF); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Do not freeze. **Protect from light.**

17 PATIENT COUNSELING INFORMATION

[*See FDA-Approved Patient Labeling*]

Instruct patients that the usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

In approximately 30% of patients in clinical trials, laxation was reported within 30 minutes of a dose of RELISTOR; therefore, advise patients to be within close proximity to toilet facilities once the drug is administered.

Instruct patients not to continue taking RELISTOR if they experience severe or persistent diarrhea. Instruct patients that common side effects of RELISTOR include transient abdominal pain, nausea and vomiting.

Instruct patients not to continue taking RELISTOR and to promptly notify their physician if they experience severe, persistent, and/or worsening abdominal symptoms because these could be symptoms of intestinal perforation [*see Warnings and Precautions (5.2)*].

Instruct patients to discontinue RELISTOR if they stop taking their opioid pain medication.

PATIENT INFORMATION

RELISTOR® *[rel' - i - store]*
(methylnaltrexone bromide)
Subcutaneous Injection

Read the Patient Information that comes with RELISTOR before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is RELISTOR?

RELISTOR is a prescription medicine used to treat constipation that is caused by prescription pain medicines, called opioids, in patients receiving supportive care for their advanced illness, when other medicines for constipation, called laxatives, have not worked well enough.

Who should not take RELISTOR?

Do not take RELISTOR if you have or may have a blockage in your intestines called a mechanical bowel obstruction. Symptoms of this blockage are vomiting, stomach pain, and swelling of your abdomen. Talk to your healthcare provider if you have any of these symptoms before taking RELISTOR.

What should I tell my healthcare provider before taking RELISTOR?

Tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if RELISTOR can harm your unborn baby. If you become pregnant while using RELISTOR, tell your healthcare provider right away.
- are breast-feeding or plan to breast-feed. It is not known if RELISTOR passes into your breast milk.
- have kidney problems.

Tell your healthcare provider about all medicines you take. Continue taking your other medicines for constipation unless your healthcare provider tells you to stop taking them.

How should I take RELISTOR?

- Take RELISTOR exactly as your healthcare provider tells you.
- Take RELISTOR by an injection under the skin (subcutaneous injection) of the upper arm, abdomen, or thigh.
- Do not take more than one dose in a 24-hour period.
- Most patients have a bowel movement within a few minutes to a few hours after taking a dose of RELISTOR.
- If you stop taking your prescription pain medicine, check with your healthcare provider before continuing to take RELISTOR.
- If you take more RELISTOR than prescribed, talk to your healthcare provider right away.

See the detailed Patient Instructions for Use at the end of this Patient Information leaflet for information about how to prepare and inject RELISTOR.

What are the possible side effects of RELISTOR?

Common side effects of RELISTOR include:

- **abdominal (stomach) pain**
- **gas**
- **nausea**
- **dizziness**

- **diarrhea**
- **sweating**
- If you get diarrhea that is severe or does not stop while taking RELISTOR, stop taking RELISTOR and call your healthcare provider.
- If you get abdominal pain that is severe or will not go away, or nausea or vomiting that is new or worse, stop taking RELISTOR and call your healthcare provider.

These are not all of the possible side effects of RELISTOR. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RELISTOR?

- Store RELISTOR vials or pre-filled syringes at 68 to 77°F (20 to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

General information about RELISTOR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use RELISTOR for a condition for which it was not prescribed. Do not give RELISTOR to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about RELISTOR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about RELISTOR that is written for healthcare providers. For more information, go to WWW.RELISTOR.COM or call 1-800-934-5556.

What are the ingredients in RELISTOR?

Active ingredient: methylnaltrexone bromide
Inactive ingredients: sodium chloride, edetate calcium disodium USP, glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

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Progenics® Pharmaceuticals

Under license from:
Progenics Pharmaceuticals, Inc.
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Patient Instructions for Use of RELISTOR® VIAL AND STANDARD SYRINGE AND NEEDLE

Introduction

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a vial of RELISTOR, and a standard syringe.

The Patient Instructions for Use includes the following steps:

Before starting, read and make sure that you understand the Patient Instructions for Use. If you have any questions, talk to your healthcare provider.

Gather the supplies you will need for your injection. These include:

1. RELISTOR vial
2. 1 mL syringe with a 27-gauge needle for subcutaneous use
3. 2 alcohol swabs
4. Cotton ball or gauze
5. Adhesive bandage

Important Notes:

- **Use the syringes and needles prescribed by your healthcare provider.**
- **Do not use a RELISTOR vial more than one time, even if there is medicine left in the vial.**
- **If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period. For more information about how to store RELISTOR, see the section called "How should I store RELISTOR?" in the FDA-Approved Patient Labeling.**
- **Safely throw away RELISTOR vials after use.**

- **Do not re-use syringes or needles.**
- **To avoid needle stick injuries, do not recap used needles.**

Step 1: Choosing and preparing an injection site

1. Choose an injection site — abdomen, thighs, or upper arms. See shaded areas in Figures 1 and 2 below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.

   Figure 1. Abdomen or thigh – use these sites when injecting yourself or another person.

   Figure 2. Upper arm – use this site only when injecting another person.

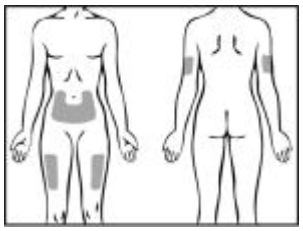

Figure 1 Figure 2

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

Figure 3

Step 2: Preparing the injection

1. Find a quiet place. Choose a flat, clean, well-lit working surface.
2. Wash your hands with soap and warm water before preparing for the injection.

3. Look at the vial of RELISTOR (Figure 1). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. If not, do not use the vial, and call your healthcare provider.

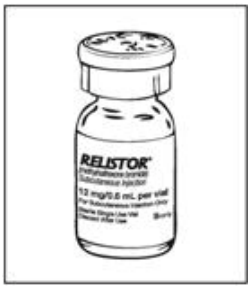

Figure 1

Step 3: Preparing the syringe

1. Remove the cap from the RELISTOR vial (Figure 2).

Figure 2

2. Wipe the rubber stopper with an alcohol swab (Figure 3).

Figure 3

3. Firmly hold the barrel of the syringe and pull the needle cap straight off (Figure 4). Do not touch the needle or allow it to touch any surface.

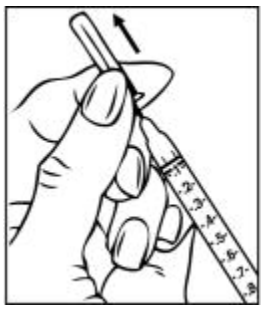

Figure 4

4. Carefully pull back the plunger to the line that matches the dose prescribed by your healthcare provider (Figure 5). For most patients, this will be the 0.4 ml mark which is an 8 mg dose or the 0.6 ml mark which is a 12 mg dose.

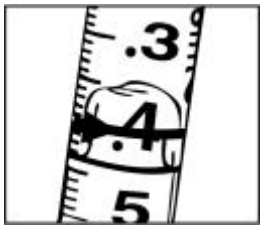

Figure 5

5. Insert the needle straight down into the rubber top of the vial (Figure 6). Do not insert it at an angle. This may cause the needle to bend or break. You will feel some resistance as the needle passes through the rubber top.

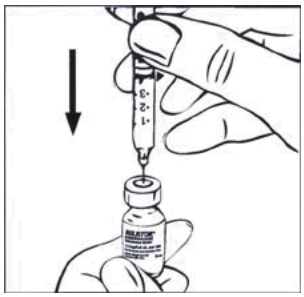

Figure 6

6. Gently push down the plunger until all of the air is out of the syringe and has gone into the vial (Figure 7).

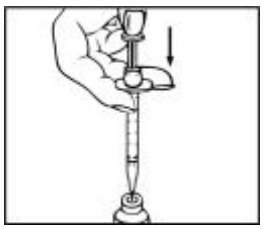

Figure 7

7. With the needle still in the vial, turn the vial and syringe upside down. Hold the syringe at eye level. Make sure the tip of the needle is in the fluid. Slowly pull back on the plunger (Figure 8) to the mark that matches your prescribed dose. For most patients, this will be the 0.4 ml mark which is an 8 mg dose or the 0.6 ml mark which is a 12 mg dose.

Figure 8

8. With the needle still in the vial, gently tap the side of the syringe to make any air bubbles rise to the top (Figure 9).

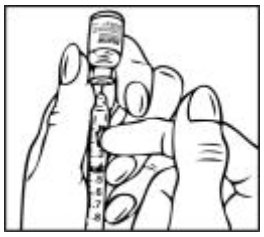

Figure 9

9. Slowly push the plunger up until all air bubbles are out of the syringe (Figure 10).

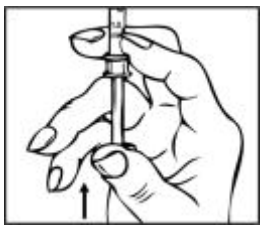

Figure 10

10. Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw the right amount of liquid back into the syringe (Figure 11).

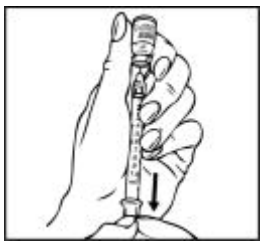

Figure 11

Check to be sure that you have the right dose of RELISTOR in the syringe.

11. Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch any surface. Safely throw away the unused medicine in the vial. See Step 5.

Step 4: Injecting RELISTOR

1. Pinch the skin around the injection site (Figure 12).

Figure 12

2. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (Figure 13).

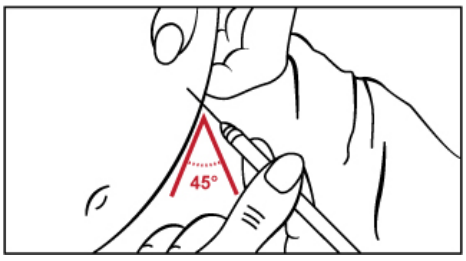

Figure 13

3. Let go of skin and slowly push down on the plunger until the syringe is empty (Figure 14).

Figure 14

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

5. Hold a cotton ball or gauze over the injection site (Figure 15). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

Figure 15

Step 5: Disposing of supplies

- **Do not re-use a syringe or needle.**
- **Do not recap a used needle.**
- Place used needle, syringes, and vials in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away (dispose of) the container. There may be state and local laws about how you should throw away used needles and syringes.

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