

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

Indications and Usage, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (1.1) [09/2014]
Dosage and Administration, Important Administration Information (2.1) [09/2014]
Dosage and Administration, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (2.2) [09/2014]
Contraindications (4) [09/2014]
Warnings and Precautions, Gastrointestinal Perforation (5.1) [09/2014]
Warnings and Precautions, Opioid Withdrawal (5.3) [09/2014]

INDICATIONS AND USAGE

RELISTOR is an opioid antagonist indicated for:

- Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain (1.1)
- Treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

Limitation of Use: Use beyond four months has not been studied (1.2)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)
- Inject in upper arm, abdomen or thigh. Rotate injection sites (2.1)
- Be within close proximity to toilet facilities once administered (2.1)
- Discontinue if treatment with opioid pain medication is also discontinued (2.1)

Opioid-induced constipation in adult patients with chronic non-cancer pain:

- RELISTOR has been shown to be efficacious in patients who have taken opioids for at least 4 weeks (2.1)
- Discontinue maintenance laxative therapy before starting RELISTOR; may resume laxatives if patients have OIC symptoms after taking RELISTOR for 3 days (2.1)
- Recommended dosage: 12 mg subcutaneously once daily (2.2)

Opioid-induced constipation in adult patients with advanced illness:

- Recommended one dose administered every other day, as needed, but no more frequently than one dose in a 24-hour period (2.1, 2.3)

Weight of Adult Patient	Subcutaneous Dose*
Less than 38 kg	0.15 mg/kg
38 kg to less than 62 kg	8 mg
62 kg to 114 kg	12 mg
More than 114 kg	0.15 mg/kg

* see full prescribing information for corresponding injection volume

- Severe renal impairment (Clcr <30 mL/min): Reduce dose by one-half (2.4)
- Prescribe pre-filled syringes only for patients requiring an 8 mg or 12 mg dose (2.5)

DOSAGE FORMS AND STRENGTHS

Single-use vial (3)

- 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x 1/2-inch needle and 1 mL syringe
- 12 mg/0.6 mL solution for subcutaneous injection with one 1 mL syringe with retractable 27 gauge x 1/2-inch needle, two alcohol swabs

Single-use pre-filled syringe (3)

- 8 mg/0.4 mL solution for subcutaneous injection
- 12 mg/0.6 mL solution for subcutaneous injection

CONTRAINDICATIONS

- Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction (4, 5.1)

WARNINGS AND PRECAUTIONS

- **Gastrointestinal perforation:** Consider the overall risk benefit in patients in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- **Severe or persistent diarrhea:** Discontinue if severe or persistent diarrhea occurs during treatment (5.2)
- **Opioid withdrawal:** Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor closely for symptoms of opioid withdrawal (5.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 1%) in adult patients with opioid-induced constipation and chronic non-cancer pain are abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills (6.1)
- The most common adverse reactions (≥ 5%) in adult patients with opioid-induced constipation and advanced illness are abdominal pain, flatulence, nausea, dizziness, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals Inc. at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Other opioid antagonists:** Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7.1)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May precipitate opioid withdrawal in a fetus (8.1)
- **Nursing Mothers:** Discontinue drug or nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

1.2 Opioid-Induced Constipation in Adult Patients with Advanced Illness

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

Limitation of Use

Use of RELISTOR beyond four months has not been studied in the advanced illness population.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

- RELISTOR is for subcutaneous use only.
- Inject RELISTOR subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
- Be within close proximity to toilet facilities once RELISTOR is administered.
- Discontinue RELISTOR if treatment with the opioid pain medication is also discontinued.
- In patients with chronic non-cancer pain and opioid-induced constipation:
 - RELISTOR has been shown to be efficacious in patients who have taken opioids for at least 4 weeks. Sustained exposure to opioids prior to starting RELISTOR may increase the patient's sensitivity to the effects of RELISTOR [see *Clinical Studies (14.1)*].
 - Discontinue all maintenance laxative therapy prior to initiation of RELISTOR. Laxative(s) can be used as needed if there is a suboptimal response to RELISTOR after three days.
 - Inject one dose every day.
 - Re-evaluate the continued need for RELISTOR when the opioid regimen is changed to avoid adverse reactions.
- In patients with advanced illness and opioid-induced constipation:
 - Inject one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

2.2 Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The recommended dosage of RELISTOR is 12 mg subcutaneously once daily [*see Clinical Studies (14.1)*].

2.3 Opioid-Induced Constipation in Adult Patients with Advanced Illness

The recommended dose of RELISTOR administered subcutaneously is 8 mg for adult patients weighing 38 kg to less than 62 kg and 12 mg for patients weighing 62 kg to 114 kg. Adult patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. The recommended dosage regimen is one dose every other day, as needed [*see Clinical Studies (14.2)*].

See Table 1 to determine the correct dose by patient weight and injection volume to be administered. The pre-filled syringe is designed to deliver a fixed dose; therefore, adult patients requiring dosing calculated on a mg/kg basis should not be prescribed pre-filled syringes.

Table 1: Weight-Based Dosing of RELISTOR and Corresponding Injection Volume for Adult Patients with Opioid-Induced Constipation and Advanced Illness

Weight of Adult Patient	Subcutaneous Dose	Injection Volume
Less than 38 kg	0.15 mg/kg	See below*
38 kg to less than 62 kg	8 mg	0.4 mL
62 kg to 114 kg	12 mg	0.6 mL
More than 114 kg	0.15 mg/kg	See below*

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

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

2.4 Use in Patients with Severe Renal Impairment

In adult patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault), dose reduction of RELISTOR by one-half is recommended [*see Use in Specific Populations (8.6)*]. No dosage adjustment is recommended for adult patients with mild to moderate renal impairment.

The pre-filled syringe is designed to deliver a fixed dose; therefore, adult patients with severe renal impairment should only be prescribed single-use vials to ensure correct dosing.

2.5 Administration and Storage

RELISTOR is a sterile, clear, and colorless to pale yellow aqueous solution. Inspect parenteral drug products visually for particulate matter and discoloration prior to

administration, whenever solution and container permit. Do not use the vial if any of these are present.

Single-use Vials

Once drawn into the 1 mL syringe with a 27-gauge x ½-inch needle, if immediate administration is not possible, store at ambient room temperature and administer within 24 hours. Discard any unused portion that remains in the vial. Advise patients concerning proper training in subcutaneous technique.

Single-use Pre-filled Syringes

Only adult patients requiring an 8 mg or 12 mg dose should be prescribed pre-filled syringes. Do not remove the pre-filled syringe from the tray until ready to administer.

3 DOSAGE FORMS AND STRENGTHS

Single-use Vial:

- 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe
- 12 mg/0.6 mL solution for subcutaneous injection, with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs

Single-use Pre-filled Syringe:

- 8 mg/0.4 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard
- 12 mg/0.6 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness 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, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom [*see Contraindications (4)*].

5.2 Severe or Persistent Diarrhea

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

5.3 Opioid Withdrawal

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR [see *Adverse Reactions (6.1)*]. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using RELISTOR in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients.

6 ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in labeling include:

- Gastrointestinal perforation [see *Warnings and Precautions (5.1)*]
- Severe or persistent diarrhea [see *Warnings and Precautions (5.2)*]
- Opioid withdrawal [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The safety of RELISTOR was evaluated in a double-blind, placebo-controlled trial in adult patients with opioid-induced constipation and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 4-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR 12 mg once daily (150 patients) or placebo (162 patients) [see *Clinical Studies (14.1)*]. After 4 weeks of double-blind treatment, patients began an 8-week open-label treatment period during which RELISTOR 12 mg was administered less frequently than the recommended dosage regimen of 12 mg once daily.

Adverse reactions in adult patients with opioid-induced constipation and chronic non-cancer pain receiving RELISTOR are shown in [Table 2](#). The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Table 2: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR in Adult Patients with Opioid-Induced Constipation and Chronic Non-Cancer Pain

Adverse Reaction	RELISTOR 12 mg once daily n = 150	Placebo n = 162
Abdominal Pain	21%	6%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	< 1%
Chills	1%	0%

* Adverse reactions occurring in $\geq 1\%$ of patients receiving RELISTOR 12 mg once daily and at an incidence greater than placebo.

During the 4-week double-blind period, in patients with opioid-induced constipation and chronic non-cancer pain that received RELISTOR 12 mg every other day, there was a higher incidence of adverse reactions, including nausea (12%), diarrhea (12%), vomiting (7%), tremor (3%), feeling of body temperature change (3%), piloerection (3%), and chills (2%) as compared to daily Relistor dosing. Use of RELISTOR 12 mg every other day is not recommended in patients with OIC and chronic non-cancer pain [see *Dosage and Administration (2.2)*]. The rates of discontinuation due to adverse reactions during the double-blind period (Study 1) were higher in the RELISTOR once daily (7%) than the placebo group (3%). Abdominal pain was the most common adverse reaction resulting in discontinuation from the double-blind period in the RELISTOR once daily group (2%).

The safety of RELISTOR was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with opioid-induced constipation and chronic non-cancer pain (Study 2). Patients were allowed to administer RELISTOR 12 mg less frequently than the recommended dosage regimen of 12 mg once daily, and took a median of 6 doses per week. A total of 624 patients (60%) completed at least 24 weeks of treatment and 477 (46%) completed the 48-week study. The adverse reactions seen in this study were similar to those observed during the 4-week double-blind period of Study 1. Additionally, in Study 2, investigators reported 4 myocardial infarctions (1 fatal), 1 stroke (fatal), 1 fatal cardiac arrest and 1 sudden death. It is not possible to establish a relationship between these events and RELISTOR.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in adult patients with opioid-induced constipation and advanced illness receiving palliative care: Study 3 included a single-dose, double-blind, placebo-controlled period, whereas Study 4 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14.2)*].

The most common ($\geq 5\%$) adverse reactions in adult patients with opioid-induced constipation and advanced illness receiving RELISTOR are shown in Table 3 below.

Table 3: Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR in Adult Patients with Opioid-Induced Constipation and Advanced Illness*		
Adverse Reaction	RELISTOR n = 165	Placebo n = 123
Abdominal Pain	29%	10%
Flatulence	13%	6%
Nausea	12%	5%
Dizziness	7%	2%
Diarrhea	6%	2%

* Adverse reactions occurring in $\geq 5\%$ of patients receiving all doses of RELISTOR (0.075, 0.15, and 0.30 mg/kg/dose) and at an incidence greater than placebo.

The rates of discontinuation due to adverse events during the double-blind placebo controlled clinical trials (Study 3 and Study 4) were comparable between RELISTOR (1%) and placebo (2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RELISTOR. Because they 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.

Gastrointestinal

Perforation, cramping, vomiting

General Disorders and Administrative Site Disorders

Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported [see *Warnings and Precautions (5.3)*].

7 DRUG INTERACTIONS

7.1 Other Opioid Antagonists

Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

7.2 Drugs Metabolized by Cytochrome P450 Isozymes

In healthy subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with RELISTOR in pregnant women. The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of intravenous methylnaltrexone during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. RELISTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal Data

Reproduction studies have been performed with methylnaltrexone administered during the period of organogenesis to rats at intravenous doses up to 25 mg/kg/day (about 20 times the MRHD of 0.2 mg/kg/day based on body surface area) and did not cause any adverse effects on embryofetal development. In rabbits, intravenous doses of methylnaltrexone up to 16 mg/kg/day (about 26 times the MRHD of 0.2 mg/kg/day based on body surface area) did not show any embryofetal toxicity. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at subcutaneous doses of methylnaltrexone up to 100 mg/kg/day (about 81 times the MRHD of 0.2 mg/kg/day based on body surface area).

8.3 Nursing Mothers

It is not known whether RELISTOR is present in human milk. However, methylnaltrexone bromide is present in rat milk. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing were observed, and the juvenile rats were found to be more sensitive to the adverse effects of methylnaltrexone bromide when compared to adult animals. Juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks had a toxicity profile similar to adult dogs [see *Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

In the double-blind studies, a total of 118 (14%) patients aged 65-74 years (79 methylnaltrexone bromide, 39 placebo) and a total of 108 (13%) patients aged 75 years or older (64 methylnaltrexone bromide, 44 placebo) were enrolled. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dose adjustment based on age is recommended.

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 as estimated by Cockcroft-Gault) [see *Dosage and Administration (2.4)*].

8.7 Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone bromide overdose were reported.

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus. Monitor for signs or symptoms of orthostatic hypotension and initiate treatment as appropriate.

If a patient on opioid therapy receives an overdose of RELISTOR, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

11 DESCRIPTION

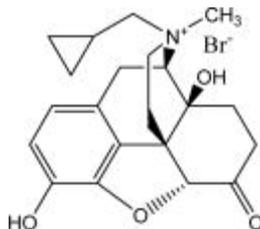
RELISTOR (methylnaltrexone bromide) injection, a mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is C₂₁H₂₆NO₄Br, and the 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 is a selective antagonist of opioid binding at the mu-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 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

Cardiac Electrophysiology

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 intravenous infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At a dose

approximately 4.3 times the maximum recommended dose (7.5 times the mean peak plasma concentration), methylnaltrexone does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, methylnaltrexone achieved peak concentrations (C_{max}) at approximately 0.5 hours. Across the range of doses from 0.15 mg/kg to 0.50 mg/kg, mean C_{max} and area under the plasma concentration-time curve (AUC) increased in a dose-proportional manner. There was no accumulation of methylnaltrexone following once-daily subcutaneous dosing of methylnaltrexone bromide 12 mg for seven consecutive days in healthy subjects.

Parameter	0.15 mg/kg single dose	12 mg single dose	12 mg at steady-state
C_{max} (ng/mL) ⁱ⁾	117 (32.7)	140 (35.6)	119 (27.2)
t_{max} (hr) ⁱⁱ⁾	0.5 (0.25-0.75)	0.25 (0.25-0.5)	0.25 (0.25-0.5)
AUC ₂₄ (ng·hr/mL) ⁱ⁾	175 (36.6)	218 (28.3)	223 (28.2)

ⁱ⁾ Expressed as mean (SD).

ⁱⁱ⁾ Expressed as median (range).

Distribution

The steady-state volume of distribution (V_{ss}) of methylnaltrexone is approximately 1.1 L/kg. The fraction of methylnaltrexone bound to human plasma proteins is 11.0% to 15.3%, as determined by equilibrium dialysis.

Elimination

Following intravenous administration of 0.3 mg/kg, the total clearance of methylnaltrexone is approximately 10.5 ± 1.5 mL/min/kg, with renal clearance of 6.37 ± 3.0 mL/min/kg. The terminal half-life ($t_{1/2}$) is approximately 8 hours.

Metabolism

In a mass balance study, approximately 44% of the administered radioactivity was recovered in the urine over 24 hours 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.

After 12 mg once daily dosing the mean AUC₀₋₂₄ ratio of metabolites to methylnaltrexone at steady-state was 30%, 19%, and 9% for methylnaltrexone sulfate, methyl-6 α -naltrexol, and methyl-6 β -naltrexol, respectively. Methyl-6 α -naltrexol, and methyl-6 β -naltrexol are active mu-opioid receptor antagonists and methylnaltrexone sulfate is a weak mu-opioid receptor antagonist.

Methylnaltrexone is conjugated by sulfotransferase SULT1E1 and SULT2A1 isoforms to methylnaltrexone sulfate. Conversion to methyl-6-naltrexol isomers is mediated by aldo-keto reductase 1C enzymes.

Excretion

After intravenous administration, approximately half of the dose was excreted in the urine (53.6%) and 17.3% of administered dose was excreted in the feces up to 168 hours postdose. Methylnaltrexone is excreted primarily as the unchanged drug in the urine and feces. Active renal secretion of methylnaltrexone is suggested by renal clearance of methylnaltrexone that is approximately 4-5 fold higher than creatinine clearance.

Specific Populations

Age: Geriatric Population

A study was conducted to characterize the pharmacokinetics of methylnaltrexone after a single dose of 24 mg methylnaltrexone via intravenous infusion over 20 min in healthy adults between 18 and 45 years of age and in healthy adults aged 65 years and older. In elderly subjects (mean age 72 years old), mean clearance was about 20% lower (56 L/h versus 70 L/h) and AUC _{∞} was 26% higher than in subjects between 18 and 45 years of age (mean age 30 years old).

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. Severe renal impairment decreased the renal clearance of methylnaltrexone by 8- to 9-fold and resulted in a 2-fold increase in total methylnaltrexone exposure (AUC). Mean C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Hepatic impairment

The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone has been studied in patients with Child-Pugh Class A (n=8) and B (n=8), 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.

Drug Interactions

In vitro, methylnaltrexone did not significantly inhibit or induce the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP3A4.

In vitro, methylnaltrexone did not induce the enzymatic activity of CYP2E1.

In vitro studies suggested that methylnaltrexone was a substrate of Organic Cation Transporter 1 but not a substrate of Organic Anion Transporter 1 or P-glycoprotein.

Cimetidine

A clinical drug interaction study in healthy adult subjects evaluated the effects of cimetidine, a drug that inhibits the active renal secretion of organic cations, on the pharmacokinetics of methylnaltrexone (24 mg administered as an IV infusion over 20 minutes). A single dose of methylnaltrexone was administered before cimetidine dosing and with the last dose of cimetidine (400 mg every 8 hours for 6 days). Mean C_{max} and AUC of methylnaltrexone increased by 10% with concomitant cimetidine administration. The renal clearance of methylnaltrexone decreased about 40%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year oral carcinogenicity studies have been conducted with methylnaltrexone in CD-1 mice at doses up to 200 mg/kg/day (about 81 times the maximum recommended human (MRHD) dose of 0.2 mg/kg/day based on body surface area) in males and 400 mg/kg/day (about 162 times the MRHD of 0.2 mg/kg/day based on body surface area) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 243 times the MRHD of 0.2 mg/kg/day based on body surface area). Oral administration of methylnaltrexone for 104 weeks did not produce tumors in mice and rats.

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 122 times the MRHD of 0.2 mg/kg/day based on 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

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 μ M concentrations, respectively).

Methylnaltrexone bromide had a hERG IC_{50} of $> 1000 \mu$ M. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 μ M) 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 μ M)

did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 μ M) 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 intravenous 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, intravenous. A thorough QTc assessment was conducted in humans [see *Clinical Pharmacology (12.2)*].

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 2.4 and 8 times, respectively, the MRHD of 0.2 mg/kg/day based on body surface area). Similar adverse clinical signs were seen in adult rats at 20 mg/kg/day (about 16 times the MRHD of 0.2 mg/kg/day based on body surface area). Juvenile rats were found to be more sensitive to the toxicity of methylnaltrexone bromide 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 0.8 and 4 times respectively, the MRHD of 0.2 mg/kg/day based on body surface area).

Juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks had a toxicity profile similar to adult dogs. Following intravenous 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 54 times the MRHD of 0.2 mg/kg/day based on 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 14 times the MRHD of 0.2 mg/kg/day based on body surface area).

14 CLINICAL STUDIES

14.1 Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in patients with chronic non-cancer pain were evaluated in a randomized, double-blind, placebo-controlled study (Study 1). This study compared 4-week treatment of RELISTOR 12 mg once daily with placebo.

A total of 312 patients (150 RELISTOR 12 mg once daily, 162 placebo) were enrolled and treated in the double-blind period. Patients had a history of chronic non-cancer pain for which they were taking opioids. The majority of patients had a primary diagnosis of back pain; other primary diagnoses included joint/extremity pain, fibromyalgia, neurologic/neuropathic pain, and rheumatoid arthritis. Prior to screening, patients had been receiving opioid therapy for pain for ≥ 1 month (median daily baseline oral morphine equivalent dose = 161 mg) and had opioid-induced constipation (< 3 spontaneous bowel movements per week during the screening period). Constipation due to opioid use had to be associated with 1 or more of the following: A Bristol Stool Form Scale score of 1 or 2 for at least 25% of the bowel movements (BM), straining during at least 25% of the BMs or a sensation of incomplete evacuation after at least 25% of the BMs.

Patients were required to be on a stable opioid regimen (daily dose ≥ 50 mg of oral morphine equivalents per day) for at least 2 weeks before the screening visit and received their opioid medication during the study as clinically needed. The median duration of opioid-induced constipation at baseline was 59 months (4.9 years). The median patient age at baseline was 49 years, 62% were females and 90% were Caucasian.

Eligible patients were required to discontinue all previous laxative therapy and use only the study-permitted rescue laxative (bisacodyl tablets). If patients did not have a bowel movement for 3 consecutive days during the study, they were permitted to use rescue medication (up to 4 bisacodyl tablets taken orally once during a 24-hour period). Rescue laxatives were prohibited until at least 4 hours after taking an injection of study medication.

The primary endpoint was the proportion of patients with ≥ 3 spontaneous bowel movements (SBMs) per week during the 4-week double-blind period. A SBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours. [Table 5](#) presents the proportion of subjects with weekly SBM rate ≥ 3 during the double-blind treatment period in the modified intent-to-treat (mITT) population, which included all randomized subjects who received at least one dose of double-blind study medication.

As shown in [Table 5](#), 59% of subjects in the RELISTOR 12 mg once daily treatment group had ≥ 3 SBMs/week compared to 38% in the placebo treatment group during the 4-week double-blind period.

Table 5: Primary Endpoint by Treatment Group in the mITT Population

Endpoint	Treatment	N	n (%)	Percent Difference ^a (2-sided 95% CI)	P-value ^b
Proportion of patients with ≥ 3 SBMs/week during the double-blind period	RELISTOR 12 mg once daily	150	88 (59%)	20% (10%, 31%)	< 0.001
	Placebo	162	62 (38%)		

CI = confidence interval; mITT = modified intent-to-treat;

^aDifference for active treatment vs. placebo;

^bp-Value for active treatment vs. placebo based on 2-sided Chi-square test.

Following the first dose, 33% of patients in the RELISTOR 12 mg once daily treatment group had a SBM within 4 hours and approximately half of patients had a SBM prior to the second dose of RELISTOR.

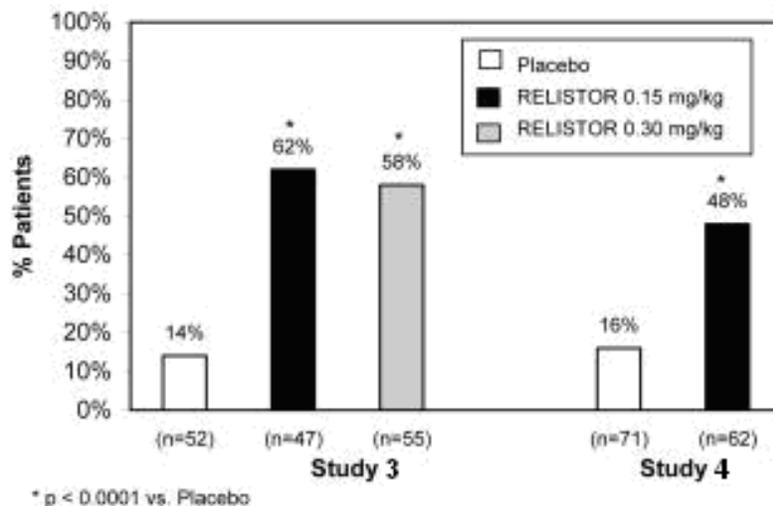
14.2 Opioid-Induced Constipation in Adult Patients with Advanced Illness

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 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 3 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 4 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%).

Durability of Response

Durability of response was explored in Study 4, and 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 3, and in two open-label extension studies (Study 3EXT and Study 4EXT) 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 3, 3EXT, and 4EXT, respectively. Laxation response was also explored in

this open-label setting and appeared to be maintained over the course of 3 to 4 months of open-label treatment.

Opioid Use and Pain Scores

No relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients was identified in exploratory analyses of 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

How Supplied

NDC NUMBER	PACK SIZE	CONTENTS
65649-551-02	1 vial per carton	one 12 mg/0.6 mL single-use vial
65649-553-05	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
65649-552-04	7 pre-filled syringes per carton	seven 8 mg/0.4 mL single-use pre-filled syringes with needle guard system
65649-551-03	7 pre-filled syringes per carton	seven 12 mg/0.6 mL single-use pre-filled syringes with needle guard system
65649-551-07	1 pre-filled syringe per carton	one 12mg/0.6 mL single-use pre-filled syringe with needle guard system

Storage

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

Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration

Advise all patients to:

- Inject RELISTOR subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
- Safely dispose of needles by following the sharps disposal recommendations described in the RELISTOR Instructions for Use.
- Be within close proximity to toilet facilities once RELISTOR is administered.
- Discontinue RELISTOR if treatment with the opioid pain medication is also discontinued.

Advise chronic non-cancer pain patients receiving RELISTOR for opioid-induced constipation to:

- Discontinue all maintenance laxative therapy prior to initiation of RELISTOR. Laxative(s) can be used as needed if there is a suboptimal response to RELISTOR after three days.
- Inject one dose every day.
- Inform their healthcare provider if their opioid regimen is changed, to avoid adverse reactions, such as diarrhea.

Advise patients with advanced illness receiving RELISTOR for opioid-induced constipation to:

- Inject one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

Gastrointestinal Perforation

Advise patients to discontinue RELISTOR and to promptly seek medical attention if they develop unusually severe, persistent, or worsening abdominal pain [*see Warnings and Precautions (5.1)*].

Severe or Persistent Diarrhea

Advise patients to discontinue RELISTOR if they experience severe or persistent diarrhea.

Opioid Withdrawal

Advise patients that symptoms consistent with opioid withdrawal may occur while taking RELISTOR, including sweating, chills, diarrhea, abdominal pain, anxiety, and yawning [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1)*].

Pregnancy

Advise females of reproductive potential, who become pregnant or are planning to become pregnant that the use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood brain barrier.

Nursing

Advise females who are nursing against breastfeeding during treatment with RELISTOR due to the potential for opioid withdrawal in nursing infants.

MEDICATION GUIDE
RELISTOR® (rel - i - store)
(methylnaltrexone bromide)
Subcutaneous Injection

Read this Medication Guide before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about RELISTOR?

RELISTOR can cause serious side effects, including:

- **Tear in your stomach or intestinal wall (perforation).** Stomach pain that is severe can be a sign of a serious medical condition. If you get stomach pain that does not go away, stop taking RELISTOR and get emergency medical help right away.
- **Diarrhea that is severe or that will not go away.** Stop using RELISTOR and call your healthcare provider if you get diarrhea that is severe or that does not go away during treatment with RELISTOR.
- **Opioid withdrawal.** You may have symptoms of opioid withdrawal during treatment with RELISTOR including sweating, chills, diarrhea, stomach pain, anxiety, and yawning. Tell your healthcare provider if you have any of these symptoms.

What is RELISTOR?

RELISTOR is a prescription medicine used to treat constipation that is caused by prescription pain medicines called opioids, in adults:

- with long-lasting (chronic) pain that is not caused by cancer
- receiving treatment for advanced illness, when other medicines for constipation have not worked well enough

It is not known if RELISTOR is safe and effective if used for longer than 4 months in people with advanced illness.

It is not known if RELISTOR is safe and effective in children.

Who should not use RELISTOR?

Do not use RELISTOR if you have a bowel blockage (intestinal obstruction) or have a history of bowel blockage.

What should I tell my healthcare provider before using RELISTOR?

Before you start using RELISTOR, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have any stomach or bowel (intestines) problems, including stomach ulcer, Crohn's disease, diverticulitis, cancer of the stomach or bowel, or Ogilvie's syndrome
- are pregnant or plan to become pregnant. Taking RELISTOR during pregnancy may cause opioid withdrawal symptoms in your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with RELISTOR.
- are breastfeeding or plan to breastfeed. It is not known if RELISTOR passes into your breast milk. Taking RELISTOR while you are breastfeeding may cause opioid withdrawal in your baby. You and your healthcare provider should decide if you will take RELISTOR or breastfeed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use RELISTOR?

See the detailed Instructions for Use that comes with RELISTOR for information about how to prepare and inject RELISTOR, and properly throw away (dispose of) used needles and syringes the right way.

- RELISTOR is injected under the skin (subcutaneous injection) of the upper arm, stomach-area (abdomen), or thigh.
- Inject RELISTOR exactly as your healthcare provider tells you.
- Stay close to a toilet after using RELISTOR.
- Stop using RELISTOR if you stop taking your prescription opioid pain medicine. Tell your healthcare provider if your pain medication changes.
- If you take too much RELISTOR, call your healthcare provider or go to the nearest emergency room right away.
- **If you use RELISTOR for long-lasting (chronic) pain that is not caused by cancer:**
 - RELISTOR has been shown to be effective in people who have taken opioid pain medicines for at least 4 weeks to treat long-lasting (chronic) pain not caused by cancer.
 - Stop taking other laxatives before you start treatment with RELISTOR. You may use other laxatives if RELISTOR does not work after 3 days of treatment.
 - Inject 1 dose of RELISTOR each day.
- **If you use RELISTOR and are receiving treatment for advanced illness:**
 - Inject 1 dose of RELISTOR every other day, as needed. You should not inject more than 1 dose of RELISTOR in a 24-hour period.

What are the possible side effects of RELISTOR?

See “What is the most important information I should know about RELISTOR?”

- **The most common side effects of RELISTOR in people with long-lasting (chronic) pain that is not caused by cancer include:** stomach-area (abdomen) pain, nausea, diarrhea, sweating, hot flush, tremor, and chills.
- **The most common side effects of RELISTOR in people receiving treatment for their advanced illness include:** stomach-area (abdomen) pain, gas, nausea, dizziness, and diarrhea.

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

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

You may also report side effects to Salix Pharmaceuticals at 1-800-508-0024.

How should I store RELISTOR?

- Store RELISTOR vials and pre-filled syringes at room temperature between 68°F to 77°F (20°C 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.

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

General information about RELISTOR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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. You can ask your pharmacist or healthcare provider for information about RELISTOR that is written for health professionals.

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.

Manufactured for: Salix Pharmaceuticals, Inc., Raleigh, NC 27615

Under license from: Progenics Pharmaceuticals, Inc., Tarrytown, NY 10591

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

Please see www.salix.com for patent information. For more information, go to www.RELISTOR.com or call 1-800-508-0024.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: September 2014

Instructions for Use

RELISTOR® (rel-i-store) (methylalntrexone bromide) Subcutaneous Injection

Pre-filled Syringe

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Important information:

- **Do not** use a RELISTOR pre-filled syringe and attached needle more than 1 time, even if there is medicine left in the syringe. **See Step 4 “Dispose of used pre-filled syringes and needles.”**
- Safely throw away RELISTOR pre-filled syringes and attached needle after use.
- To avoid needle-stick injuries, **do not** recap used needles.
- Avoid touching the trigger fingers of the RELISTOR pre-filled syringe to keep from activating the needle guard (safety device) too soon. The needle guard is activated by pressure from the plunger on the trigger fingers (See [Figure A](#)).

Gather the supplies you will need for your injection (See [Figure A](#)). These include:

- 1 RELISTOR pre-filled syringe with attached needle
- 1 alcohol swab
- 1 cotton ball or gauze
- 1 adhesive bandage
- a container to dispose of used pre-filled syringes and needles. See [Step 4: “Dispose of used pre-filled syringes and needles.”](#)

Pre-filled Syringe Parts

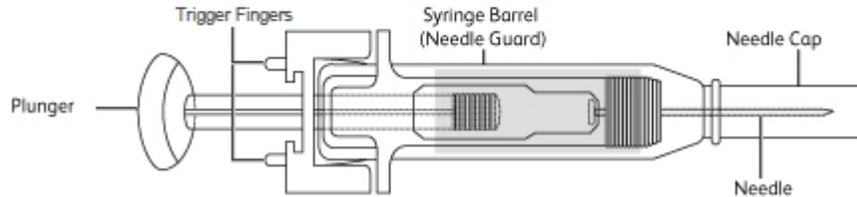


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your stomach-area (abdomen), thighs, or upper arms. See the shaded areas in Figures B and C 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 B Abdomen or thigh – use these sites when injecting yourself or another person.

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

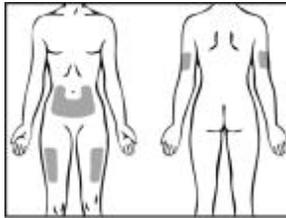


Figure B **Figure C**

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



Figure D

Step 2: Prepare the pre-filled syringe

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the pre-filled syringe of RELISTOR (See Figure E). Make sure that the dose prescribed by your healthcare provider matches the dose on the pre-filled syringe label. Look at the plunger rod of the syringe. If the dose prescribed by your healthcare provider is 8 mg, the plunger rod will be yellow; if the prescribed dose is 12 mg, the plunger rod of the syringe will be dark blue (See Figure E).

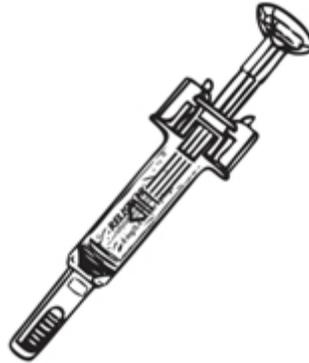


Figure E

- The liquid in the pre-filled syringe should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the pre-filled syringe if it looks discolored, cloudy, or has any particles.

- Use one hand to firmly hold the barrel of the pre-filled syringe. Use your other hand to pull the needle cap straight off (Figure F). Do not touch the needle or allow it to touch anything.



Figure F

Step 3: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure G).



Figure G

- Use your other hand to hold the pre-filled syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (See Figure H).

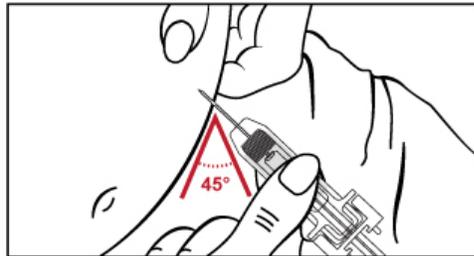


Figure H

- Let go of the skin and slowly push the plunger in with your thumb until the pre-filled syringe is empty (See Figure I). This will release the needle guard (safety device).



Figure I

- Continue to hold pressure on the plunger with your thumb and quickly pull the needle out of the skin. Be careful to keep the needle at the same angle as it was inserted. Remove your thumb from the plunger to allow the protective sleeve to cover the needle (See Figure J). There may be a little bleeding at the injection site.

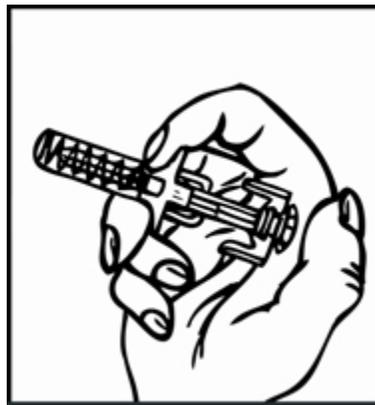


Figure J

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



Figure K

Step 4: Dispose of used pre-filled syringes and needles

- **Do not** re-use the pre-filled syringe and attached needle.
- To avoid needle-stick injuries, **do not** recap used needles.
- Put your used pre-filled syringes and attached needles in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- If you have any questions, talk to your healthcare provider or pharmacist.

How should I store RELISTOR?

- Store pre-filled syringes at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:



Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics[®]
Pharmaceuticals

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised: SEP 2014

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

See www.salix.com for patent information.

Instructions for Use

RELISTOR® (rel-i-store) (methylalntrexone bromide) Subcutaneous Injection

Vial and Syringe with Retractable Needle in Tray

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a RELISTOR tray containing a syringe with a retractable needle. A retractable needle is one that is pulled back so that it is covered after use, to prevent needle-stick injury.

Important information:

- **Do not** use a RELISTOR vial more than 1 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, carefully recap the needle and keep the syringe at room temperature for up to 24 hours. For more information about how to store RELISTOR, see the section called "**How should I store RELISTOR?**" at the end of this Instructions for Use.
- Safely throw away RELISTOR vials after use.
- **Do not** reuse syringes and needles. **See Step 5: "Dispose of used syringes and needles"** for information about how to safely throw away used needles and syringes.
- To avoid needle-stick injuries, **do not** recap used needles.

Your tray should include (See [Figure A](#)):

- 1 RELISTOR vial
- 1 1 mL syringe with retractable needle (VanishPoint®)
- 2 alcohol swabs

You will also need:

- 1 cotton ball or gauze
- 1 adhesive bandage

- a container to dispose of your used syringes and needles. See [Step 5: "Dispose of used syringes and needles."](#)

Vial and Syringe Parts

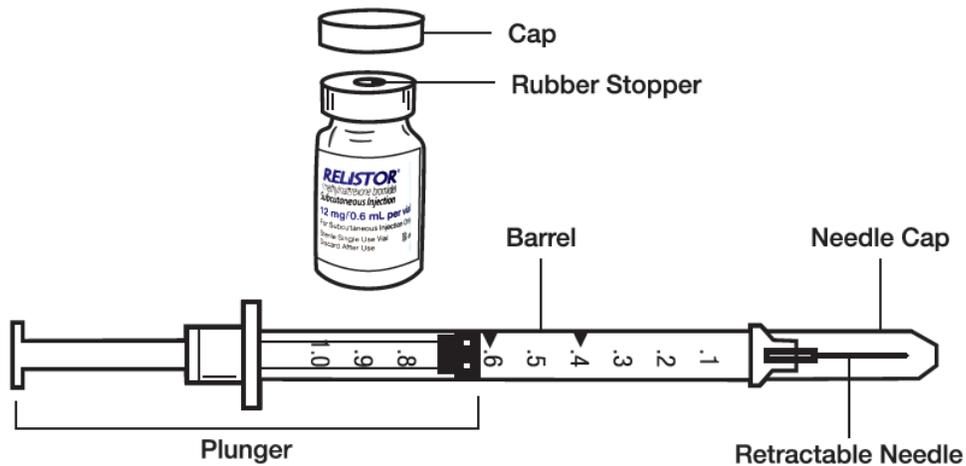


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your stomach-area (abdomen), thighs, or upper arms. See the shaded areas in Figures B and C 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 B Abdomen or thigh – use these sites when injecting yourself or another person.

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

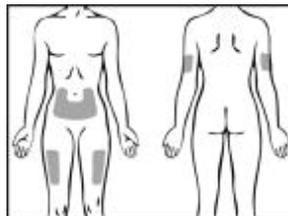


Figure B Figure C

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



Figure D

Step 2: Prepare the injection

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the vial of RELISTOR (See Figure E). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the vial if it looks discolored, cloudy, or has any particles.



Figure E

Step 3: Prepare the syringe

- Remove the cap from the vial containing RELISTOR (See Figure F).



Figure F

- Wipe the rubber stopper with an alcohol swab (See Figure G).



Figure G

- Firmly hold the barrel of the syringe with one hand. With your other hand, pull the needle cap straight off (See Figure H). Do not touch the needle or allow it to touch anything.

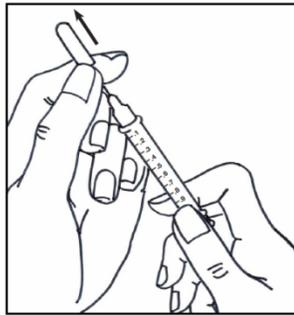


Figure H

- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider (See Figures I and J). For most people, 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.

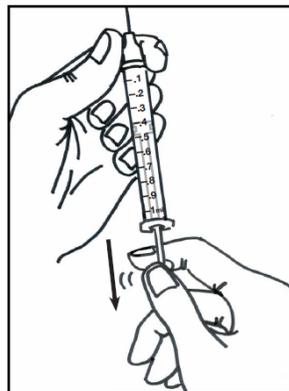


Figure I

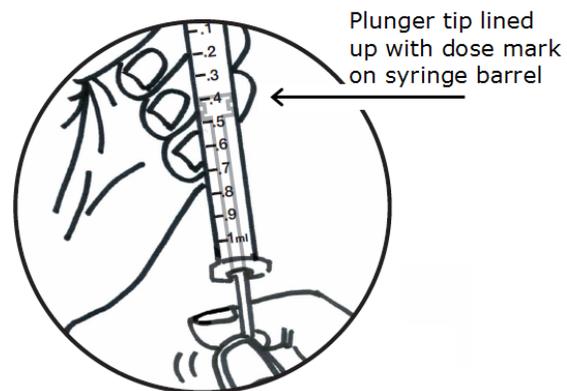


Figure J

- Use one hand to hold the vial steady. Use your other hand to insert the needle straight down into the rubber top of the RELISTOR vial (See Figure K). 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.

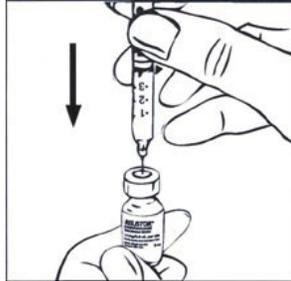


Figure K

- Gently push down on the plunger until you feel resistance, and most of the air has gone from the syringe into the vial (See Figure L). Stop pushing down on the plunger when you feel resistance. If you continue to push down on the plunger when you feel resistance, the needle will pull back (retract) into the syringe barrel.

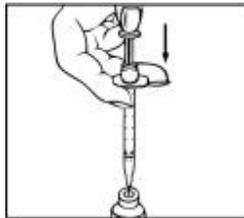


Figure L

- 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 (See Figure M) until the tip lines up with the mark that matches your prescribed dose. For most people, 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 M

- You may see some fluid or bubbles inside the vial when the syringe is filled. This is normal.
- With the needle still in the vial, gently tap the syringe to make any air bubbles rise to the top (See Figure N).



Figure N

- Gently push the plunger up until all air bubbles are out of the syringe (See Figure O). A small air bubble may stay in the syringe. This is okay and it will not affect the dose of medicine in the syringe.

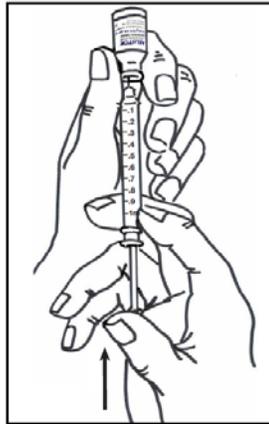


Figure O

- 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 (See Figure P).



Figure P

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

- Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch anything. Safely throw away the vial with any unused medicine.

Step 4: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure Q).



Figure Q

- Use your other hand to hold the syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick “dart-like” motion (See Figure R).

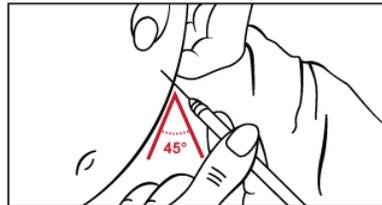


Figure R

- Let go of the skin and slowly push in on the plunger past the resistance point, until the syringe is empty and you hear a click (See Figure S).



Figure S

- The click sound means that the needle (See Figure T) has been pulled back (retracted) into the syringe barrel (See Figure U). You can now remove the syringe from your skin.

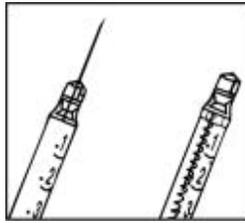


Figure T Figure U

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



Figure V

Step 5: Dispose of used syringes and needles

- **Do not** re-use syringes or needles.
- To avoid needle-stick injuries, **do not** recap used needles.
- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- If you have any questions, talk to your healthcare provider or pharmacist.

How should I store RELISTOR?

- Store RELISTOR vials at room temperature between 68°F to 77°F (20°C 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.

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:



Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics[®]

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised: SEP 2014

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

See www.salix.com for patent information.

Instructions for Use

RELISTOR[®] (rel-i-store) (methyl naltrexone bromide) Subcutaneous Injection

Vial

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Important information:

- Use the syringes and needles prescribed by your healthcare provider.
- **Do not** use a RELISTOR vial more than 1 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, carefully recap the needle and keep the syringe at room temperature for up to 24 hours. For more information about how to store RELISTOR, see the section [“How should I store RELISTOR?”](#) at the end of this Instructions for Use.
- Safely throw away RELISTOR vials after use.
- **Do not** re-use syringes or needles. See [Step 5 “Dispose of used syringes and needles”](#) for information about how to safely throw away used needles and syringes.
- To avoid needle-stick injuries, **do not** recap used needles.

Gather the supplies you will need for your injection (See [Figure A.](#)). These include:

- 1 RELISTOR vial
- 1 1 mL syringe with a 27-gauge, ½ inch needle for subcutaneous use
- 2 alcohol swabs
- 1 cotton ball or gauze
- 1 adhesive bandage
- a container to dispose of used syringes and needles. See [Step 5: “Dispose of used syringes and needles.”](#)

Vial and Syringe Parts

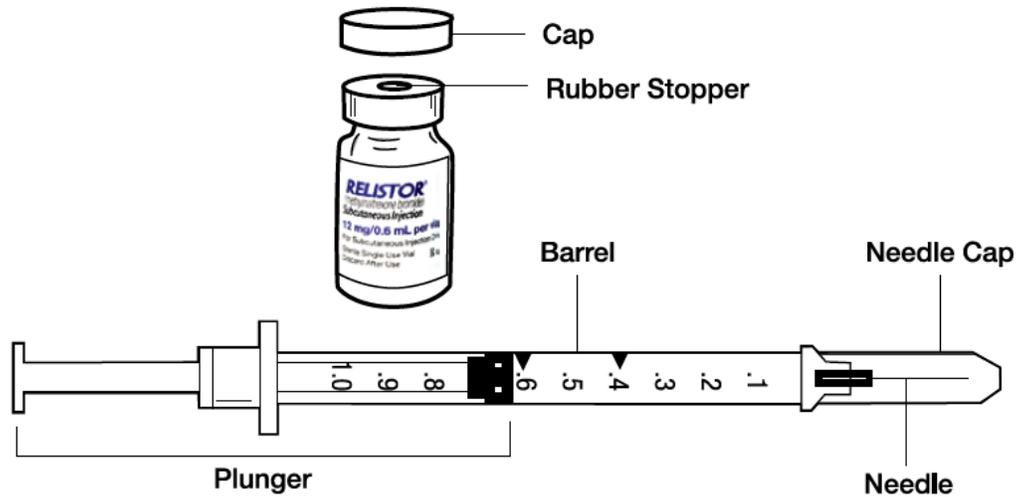


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your stomach-area (abdomen), thighs, or upper arms. See the shaded areas in Figures B and C 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 B Abdomen or thigh – use these sites when injecting yourself or another person.

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

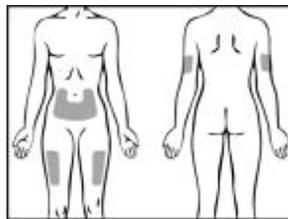


Figure B

Figure C

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



Figure D

Step 2: Prepare the injection

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the vial of RELISTOR (See Figure E). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the vial if it looks discolored, cloudy, or has any particles.



Figure E

Step 3: Prepare the syringe

- Remove the cap from the RELISTOR vial (See Figure F).



Figure F

- Wipe the rubber stopper with an alcohol swab (See Figure G).



Figure G

- Firmly hold the barrel of the syringe with one hand. With your other hand, pull the needle cap straight off (See Figure H). Do not touch the needle or allow it to touch anything.

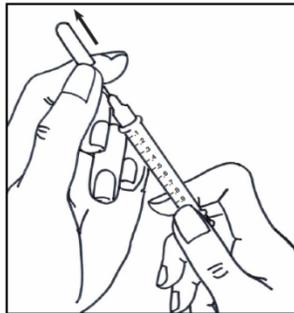


Figure H

- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider (See Figures I and J). For most people, 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.

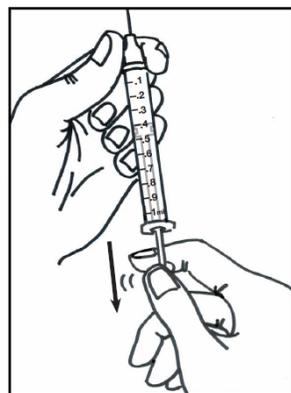


Figure I

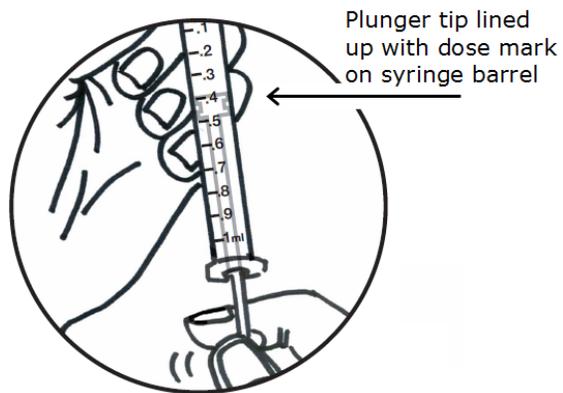


Figure J

- Use one hand to hold the vial steady. Use your other hand to insert the needle straight down into the rubber top of the vial (See Figure K). 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.

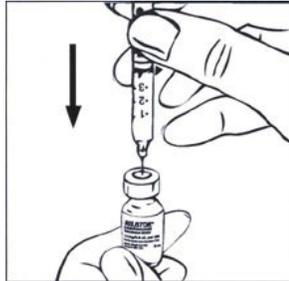


Figure K

- Gently push down the plunger until all of the air has gone from the syringe into the vial (See Figure L).

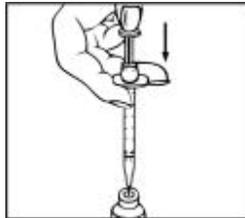


Figure L

- 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 (See Figure M) until the tip lines up with the mark that matches your prescribed dose. For most people, 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 M

- You may see some fluid or bubbles inside the vial when the syringe is filled. This is normal.
- With the needle still in the vial, gently tap the side of the syringe to make any air bubbles rise to the top (See Figure N).



Figure N

- Slowly push the plunger up until all air bubbles are out of the syringe (See Figure O). A small air bubble may stay in the syringe. This is okay and it will not affect the dose of medicine in the syringe.

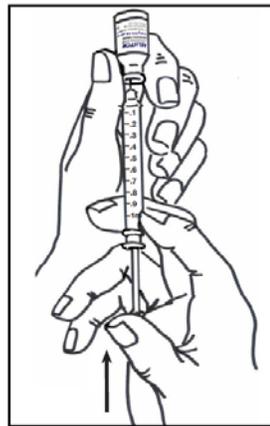


Figure O

- 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 (See Figure P).



Figure P

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

- Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch anything. Safely throw away the vial with any unused medicine.

Step 4: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure Q).



Figure Q

- Use your other hand to hold the syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (See Figure R).

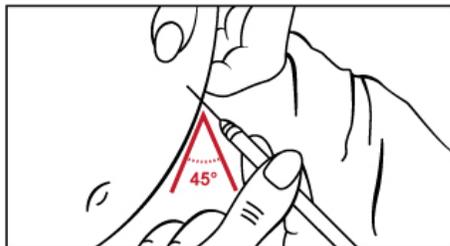


Figure R

- Let go of the skin and slowly push in on the plunger until the syringe is empty (Figure S).



Figure S

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



Figure T

Step 5: Dispose of used syringes and needles

- **Do not** re-use a syringe or needle.
- To avoid needle-stick injuries, **do not** recap a used needle.
- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
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