

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® (methylaltraxone bromide) tablets, for oral use
RELISTOR® (methylaltraxone bromide) injection, for subcutaneous use
Initial U.S. Approval: 2008

Indications and Usage (1.1)	07/2016
Dosage and Administration (2.1, 2.2)	07/2016
Dosage and Administration (2.4, 2.5)	01/2017

INDICATIONS AND USAGE

- RELISTOR is an opioid antagonist. RELISTOR tablets and RELISTOR injection are indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. (1.1)
- RELISTOR injection is indicated for the treatment of OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. (1.2)
 - Limitations of Use: Use beyond four months has not been studied in the advanced illness population. (1.2)

DOSAGE AND ADMINISTRATION

Administration Instructions (2.1)

- Be within close proximity to toilet facilities once administered.
- Discontinue if treatment with opioid pain medication is also discontinued.
- In adult patients with chronic non-cancer pain and OIC:
 - RELISTOR has been shown to be efficacious in patients who have taken opioids for at least 4 weeks.
 - Discontinue all maintenance laxative therapy before starting RELISTOR; may resume laxatives if there is a suboptimal response to RELISTOR after 3 days.
 - Re-evaluate the continued need for RELISTOR when opioid regimen is changed to avoid adverse reactions.
- In patients with chronic non-cancer pain and OIC, take RELISTOR tablets with water on an empty stomach at least 30 minutes before the first meal of the day.

Dosing

- For OIC in adult patients with chronic non-cancer pain (2.2):
 - RELISTOR tablets: The recommended dosage is 450 mg once daily in the morning.
 - RELISTOR injection: The recommended dosage is 12 mg subcutaneously once daily.
- For OIC in adult patients with advanced illness (2.3):
 - The pre-filled syringe is only for patients who require a RELISTOR injection dose of 8 mg or 12 mg. Use the vial for patients who require other doses of RELISTOR injection.
 - RELISTOR injection: See Table 1 in the full prescribing information for the recommended dosage; administer one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

Dosage Adjustment

- See full prescribing information dosage adjustment in renal or hepatic impairment by indication. (2.4, 2.5)

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Preparation and Administration of RELISTOR Injection (2.6)

- For subcutaneous use only.
- Inject in upper arm, abdomen or thigh. Rotate injection sites.

DOSAGE FORMS AND STRENGTHS

- Tablets: 150 mg methylaltraxone bromide. (3)
- Injection:
 - 8 mg/0.4 mL methylaltraxone bromide in single-dose pre-filled syringe. (3)
 - 12 mg/0.6 mL methylaltraxone bromide in a single-dose pre-filled syringe, or single-dose vial. (3)

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 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 are:

OIC in adult patients with chronic non-cancer pain (6.1)

- RELISTOR tablets ($\geq 2\%$): abdominal pain, diarrhea, headache, abdominal distention, vomiting, hyperhidrosis, anxiety, muscle spasms, rhinorrhea, and chills.
- RELISTOR injection ($\geq 1\%$): abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills.

OIC in adult patients with advanced illness (6.1)

- RELISTOR injection ($\geq 5\%$): abdominal pain, flatulence, nausea, dizziness, and diarrhea.

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 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)
- Lactation:** Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

7 DRUG INTERACTIONS

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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 tablets and RELISTOR injection are indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

1.2 Opioid-Induced Constipation in Adult Patients with Advanced Illness

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

- Be within close proximity to toilet facilities once RELISTOR is administered.
- Discontinue RELISTOR if treatment with the opioid pain medication is also discontinued.
- In adult patients with chronic non-cancer pain and OIC:
 - 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.
 - Re-evaluate the continued need for RELISTOR when the opioid regimen is changed to avoid adverse reactions.
- In patients with chronic non-cancer pain and OIC, take RELISTOR tablets with water on an empty stomach at least 30 minutes before the first meal of the day.

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

- The recommended dosage of RELISTOR tablets is 450 mg taken orally once daily in the morning.
- The recommended dosage of RELISTOR injection is 12 mg administered subcutaneously once daily.

2.3 Opioid-Induced Constipation in Adult Patients with Advanced Illness

The pre-filled syringe is only for patients who require a RELISTOR injection dose of 8 mg or 12 mg. Use the vial for patients who require other doses of RELISTOR injection.

Table 1 below shows the recommended weight-based dose of RELISTOR injection and the corresponding injection volume. The recommended dosage regimen is one dose administered subcutaneously every other day, as needed. Do not administer more frequently than one dose per 24-hour period.

Table 1: Weight-Based Dosing of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC 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*

* Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL.

2.4 Dosage in Patients with Renal Impairment

The recommended dosage of RELISTOR in patients with moderate and severe renal impairment (i.e., creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault) [*see Use in Specific Populations (8.6)*], is shown below by indication:

OIC in Adult Patients with Chronic Non-Cancer Pain

- RELISTOR tablets: 150 mg once daily in the morning.
- RELISTOR injection: 6 mg administered subcutaneously once daily

OIC in Adult Patients with Advanced Illness

RELISTOR injection: The recommended dosage regimen is one dose every other day, as needed is shown in Table 2.

Table 2: Weight-Based Dosing in Moderate and Severe Renal Impairment of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC and Advanced Illness		
Weight of Adult Patient	Subcutaneous Dose	Injection Volume
Less than 38 kg	0.075 mg/kg	See below*
38 kg to less than 62 kg	4 mg	0.2 mL
62 kg to 114 kg	6 mg	0.3 mL
More than 114 kg	0.075 mg/kg	See below*

* Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.00375 and then rounding up the volume to the nearest 0.1 mL.

2.5 Dosage in Patients with Hepatic Impairment

OIC in Adult Patients with Chronic Non-Cancer Pain

- RELISTOR tablets: The recommended dosage in adult patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) is 150 mg, once daily in the morning [*see Use in Specific Populations (8.7)*].
- RELISTOR injection: If considering dose adjustment for patients with severe hepatic impairment, follow the recommendations in Table 3 [*see Use in Specific Populations (8.7)*].

Table 3: Weight-Based Dosing in Severe Hepatic Impairment of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC and Chronic Non-Cancer Pain

Weight of Adult Patient	Subcutaneous Dose	Injection Volume
Less than 38 kg	0.075 mg/kg	See below*
38 kg to less than 62 kg	4 mg	0.2 mL
62 kg to 114 kg	6 mg	0.3 mL
More than 114 kg	0.075 mg/kg	See below*

* Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.00375 and then rounding up the volume to the nearest 0.1 mL.

2.6 Preparation and Administration of RELISTOR Injection

- RELISTOR injection is for subcutaneous use only.
- Single-dose pre-filled syringes: Do not remove the pre-filled syringe from the tray until ready to administer.
- Inspect RELISTOR injection visually for particulate matter and discoloration prior to administration. RELISTOR injection is colorless to pale yellow. Discard the pre-filled syringe or vial if particulate matter or discoloration is present.
- Administer RELISTOR injection subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
- RELISTOR Single-dose vials: Once drawn into the syringe, 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.
- For patient or caregiver instructions for preparation and administration of RELISTOR injection (including recommended specifications for the syringe and needle to be used with the single-dose vial), see *Instructions for Use*.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 150 mg methylnaltrexone bromide supplied as film-coated, white, round, biconvex, debossed with “REL” on one side and plain on the other side.

Injection:

Single-dose Vial:

- 12 mg/0.6 mL methylnaltrexone bromide supplied as colorless to pale yellow solution.

Single-dose Pre-filled Syringe:

- 8 mg/0.4 mL methylnaltrexone bromide supplied as colorless to pale yellow solution.
- 12 mg/0.6 mL methylnaltrexone bromide supplied as colorless to pale yellow solution.

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 OIC 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 the 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 tablets was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 12-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR tablets 450 mg orally (200 patients) or placebo (201 patients) [*see Clinical Studies (14.1)*]. After 4 weeks of double-blind treatment administered once daily, patients continued 8 weeks of double-blind treatment on an as needed basis (but not more than once daily).

The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR tablets are shown in Table 4. Adverse reactions of abdominal pain, diarrhea, hyperhidrosis, anxiety, rhinorrhea, and chills may reflect symptoms of opioid withdrawal.

Table 4: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Tablets in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 1)

Adverse Reaction	RELISTOR Tablets n = 200	Placebo n = 201
Abdominal Pain **	14%	10%
Diarrhea	5%	2%
Headache	4%	3%
Abdominal Distention	4%	2%
Vomiting	3%	2%
Hyperhidrosis	3%	1%
Anxiety	2%	1%
Muscle Spasms	2%	1%
Rhinorrhea	2%	1%
Chills	2%	0%

* Adverse reactions occurring in at least 2% of patients receiving RELISTOR tablets 450 mg once daily and at an incidence greater than placebo.

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

The safety of RELISTOR injection was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 2) included a 4-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR injection 12 mg subcutaneously 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 injection 12 mg subcutaneously was administered less frequently than the recommended dosage regimen of 12 mg once daily.

The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR injection are shown in Table 5. The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Table 5: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Injection in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 2)

Adverse Reaction	RELISTOR Injection n = 150	Placebo n = 162
Abdominal Pain**	21%	7%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	<1%
Chills	1%	0%

* Adverse reactions occurring in at least 1% of patients receiving RELISTOR injection 12 mg subcutaneously once daily and at an incidence greater than placebo.

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

During the 4-week double-blind period, in patients with OIC and chronic non-cancer pain that received RELISTOR 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 injection 12 mg subcutaneously 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 2) 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 injection was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with OIC and chronic non-cancer pain (Study 3). Patients were allowed to administer RELISTOR injection 12 mg subcutaneously 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 2. Additionally, in Study 3, 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 injection was evaluated in two, double-blind, placebo-controlled trials in adult patients with OIC and advanced illness receiving palliative care: Study 4 included a single-dose, double-blind, placebo-controlled period, whereas Study 5 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14.2)*].

The most common adverse reactions in adult patients with OIC and advanced illness receiving RELISTOR injection are shown in Table 6 below.

Table 6: Adverse Reactions from All Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR Injection in Adult Patients with OIC and Advanced Illness* (Studies 4 and 5)		
Adverse Reaction	RELISTOR Injection 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 at least 5% of patients receiving all doses of RELISTOR injection (0.075, 0.15, and 0.3 mg/kg) and at an incidence greater than placebo

** Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness

The rates of discontinuation due to adverse reactions during the double-blind, placebo-controlled clinical trials (Study 4 and Study 5) 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 injection. Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Gastrointestinal

Perforation, cramping, vomiting

General Disorders and Administration 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 0.3 mg/kg of RELISTOR did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with RELISTOR in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriages. There are clinical considerations when RELISTOR is used by pregnant women [*see Clinical Considerations*]. In animal reproduction studies, no effects on embryofetal development were observed with the administration of intravenous methylnaltrexone bromide during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the subcutaneous maximum recommended human dose (MRHD) of 12 mg RELISTOR injection per day. The intravenous doses in rats and rabbits are about 0.5 times and 0.7 times, respectively, the oral MRHD of 450 mg/day [*see Data*]. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier.

Data

Animal Data

Reproduction studies have been performed with methylnaltrexone bromide administered during the period of organogenesis to rats at intravenous doses up to 25 mg/kg/day (about 20 times the subcutaneous MRHD of 12 mg/day based on body surface area), and did not cause any adverse effects on embryofetal development. In rabbits, intravenous doses of methylnaltrexone bromide up to 16 mg/kg/day (about 26 times the subcutaneous MRHD of 12 mg/day) did not show any embryofetal toxicity. The intravenous doses in rats (25 mg/kg/day) and rabbits (16 mg/kg/day) are about 0.5 and 0.7 times, respectively, the oral MRHD of 450 mg/day based on body surface area. 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 bromide up to

100 mg/kg/day (about 81 times the subcutaneous MRHD of 12 mg/day; about 2.2 times the oral MRHD of 450 mg/day).

8.2 Lactation

Risk Summary

There is no information regarding the presence of methylnaltrexone in human milk, the effects on the breastfed infant, or the effects on milk production. Methylnaltrexone is present in rat milk [see Data]. Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR.

Data

Radioactivity appeared in rat milk within 30 minutes of a single subcutaneous administration of radiolabeled methylnaltrexone bromide and was concentrated up to 24-fold at 8 hours after administration relative to plasma concentrations.

8.4 Pediatric Use

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

Juvenile Animal Studies

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 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

Of the total number of patients in clinical studies of RELISTOR tablets, a total of 136 patients (10%) were aged 65 years and older, while 23 (2%) were aged 75 and older. In clinical studies of RELISTOR tablets, no overall differences in effectiveness were observed. Adverse reactions were similar; however, there was a higher incidence of diarrhea in elderly patients.

Of the total number of patients in clinical studies of RELISTOR injection, a total of 226 (28%) were aged 65 years and older, while 108 (13%) were aged 75 years and older. In clinical studies of RELISTOR injection, no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dosage adjustment based on age is recommended. Monitor elderly patients for adverse reactions.

8.6 Renal Impairment

In a study of subjects with varying degrees of renal impairment receiving RELISTOR injection subcutaneously, there was a significant increase in the exposure to methylnaltrexone in subjects with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault) compared to healthy subjects [see Clinical Pharmacology (12.3)].

Therefore, a dosage reduction of RELISTOR tablets and RELISTOR injection is recommended in patients with moderate and severe renal impairment [see *Dosage and Administration* (2.4)]. No dosage adjustment of RELISTOR tablets or RELISTOR injection is needed in patients with mild renal impairment (creatinine clearance greater than 60 mL/minute as estimated by Cockcroft-Gault).

8.7 Hepatic Impairment

Tablets

In a study of subjects with varying degrees of hepatic impairment receiving a 450 mg dose of RELISTOR tablets, there was a significant increase in systemic exposure of methylnaltrexone for subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment compared to healthy subjects with normal hepatic function [see *Clinical Pharmacology* (12.3)]. Therefore, a dosage reduction of RELISTOR tablets is recommended in patients with moderate or severe hepatic impairment [see *Dosage and Administration* (2.5)]. No dosage adjustment of RELISTOR tablets is needed in patients with mild hepatic impairment (Child-Pugh Class A).

Injection

In a study of subjects with mild or moderate hepatic impairment, there was no clinically meaningful change in systemic exposure of methylnaltrexone compared to healthy subjects with normal hepatic function [see *Clinical Pharmacology* (12.3)]. Therefore, no dosage adjustment of RELISTOR injection is needed for patients with mild or moderate hepatic impairment [see *Clinical Pharmacology* (12.3)].

Patients with severe hepatic impairment were not studied. In patients with severe hepatic impairment, monitor for methylnaltrexone-related adverse reactions. If considering dosage adjustment, follow the recommendations in Table 3 [see *Dosage and Administration* (2.5)].

10 OVERDOSAGE

During clinical trials of RELISTOR administered orally and subcutaneously, one accidental case of methylnaltrexone bromide overdose was reported and no adverse events were reported as a result of the overdose.

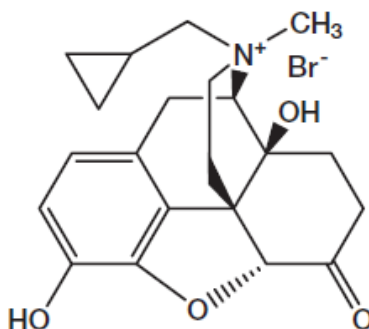
A study of healthy subjects noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus. Monitor for signs or symptoms of orthostatic hypotension and initiate treatment as appropriate.

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) is a mu-opioid receptor antagonist. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is C₂₁H₂₆NO₄Br, and the molecular weight is 436.36.

The structural formula is:



RELISTOR tablets for oral administration are film-coated and contain 150 mg of methylnaltrexone bromide (equivalent to 122.5 mg methylnaltrexone). Inactive ingredients are silicified microcrystalline cellulose, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

RELISTOR for subcutaneous administration is a sterile, clear and colorless to pale yellow aqueous solution. Each 3 mL vial contains 12 mg of methylnaltrexone bromide (equivalent to 9.8 mg of methylnaltrexone) 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 (equivalent to 6.5 mg of methylnaltrexone) 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 (equivalent to 9.8 mg of methylnaltrexone) 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.

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 (RELISTOR is

not approved for intravenous use), 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 for RELISTOR injection and 22 times the peak plasma concentration for RELISTOR tablets), methylnaltrexone does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Between the oral dosage range of 150 mg to 450 mg for RELISTOR tablets and the subcutaneous dosage range of 0.15 mg/kg to 0.50 mg/kg for RELISTOR injection, the mean C_{max} and area under the plasma concentration-time curve (AUC) of methylnaltrexone increased in a dose-proportional manner. There was no significant accumulation of methylnaltrexone following once-daily oral dosing of 450 mg RELISTOR tablets or subcutaneous dosing of 12 mg RELISTOR injection for seven consecutive days in healthy subjects.

Absorption

Tablets

Following administration of a single 450 mg dose of RELISTOR tablets in OIC patients or healthy subjects, peak concentrations (C_{max}) of methylnaltrexone were observed at approximately 1.5 hours. The absolute bioavailability of oral methylnaltrexone bromide has not been determined. The C_{max} and AUC in healthy subjects were 48.1 ng/mL and 382 ng·hr/mL, respectively, following a single 450 mg dose of RELISTOR tablets. Exposure in the OIC patient population was approximately 27% lower than in healthy subjects.

Food Effect

Administration of a single 450 mg dose of RELISTOR tablets to healthy subjects with a high fat breakfast (containing approximately 800 to 1000 total calories, with 60%, 25% and 15% of calories derived from fat, carbohydrate and protein, respectively) resulted in a decrease in the C_{max} of methylnaltrexone by 60%, the AUC by 43% and delayed the T_{max} by 2 hours [see *Dosage and Administration (2.1)*].

Injection

Following administration of RELISTOR injection subcutaneously, methylnaltrexone achieved peak concentrations (C_{max}) at approximately 0.5 hours (see Table 7).

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 to 0.75)	0.25 (0.25 to 0.5)	0.25 (0.25 to 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% to 15%, as determined by equilibrium dialysis.

Elimination

Following oral administration of a single 450 mg dose of RELISTOR tablets, concentrations of methylnaltrexone declined in multiphasic manner with a terminal half-life ($t_{1/2}$) of approximately 15 hours.

Metabolism

In an intravenous mass balance study, approximately 44% of the administered radioactivity was recovered in the urine over 24 hours with 5 distinct metabolites. 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% of total) appear to be the primary pathways of metabolism. N-demethylation of methylnaltrexone to produce naltrexone is not significant.

Systemic exposure of methylnaltrexone metabolites after oral administration of a single 450 mg dose of RELISTOR tablets are greater than the systemic exposure of methylnaltrexone metabolites after subcutaneous administration of a single 12 mg dose of RELISTOR injection. Subcutaneous administration is not subject to first-pass hepatic metabolism prior to appearance in the systemic circulation. After 12 mg subcutaneous once daily dosing the mean AUC_{0-24} 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. After 450 mg oral once daily dosing, the ratio of the mean AUC_{0-24} of metabolites to methylnaltrexone at steady-state was 79%, 38%, and 21% for methylnaltrexone sulfate, methyl-6 α -naltrexol, and methyl-6 β -naltrexol, respectively. Methylnaltrexone sulfate is a weak mu-opioid receptor antagonist; methyl-6 α -naltrexol, and methyl-6 β -naltrexol are active mu-opioid receptor antagonists.

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

In an intravenous mass balance study, approximately half of the dose was excreted in the urine (54%), and 17% of administered dose was excreted in the feces up to 168 hours postdose; however, radiolabeled recovery in this study was only 71% after 7 days. 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- to 5-fold higher than creatinine clearance.

No mass balance clinical studies were conducted with oral administration of methylnaltrexone bromide. However, following once daily dosing of 450 mg RELISTOR tablets for one week, the percentage of dose recovered in the urine as the parent methylnaltrexone was low (approximately 1% on both Day 1 and Day 7).

Specific Populations

Age: Geriatric Population

A study was conducted to characterize the pharmacokinetics of methylnaltrexone after a single dose of 24 mg methylnaltrexone bromide 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 $AUC_{0-\infty}$ was 26% higher than in subjects between 18 and 45 years of age (mean age 30 years old) [*see Use in Specific Populations (8.5)*].

Renal Impairment

Administration of a single subcutaneous dose of 0.3 mg/kg of RELISTOR injection in subjects with varying degrees of renal impairment (8 subjects each cohort) resulted in a 1.3-, 1.7- and 1.9-fold higher $AUC_{0-\infty}$ of methylnaltrexone, respectively, compared to 8 subjects with normal renal function [*see Dosage and Administration (2.4)*]. The mean C_{max} did not change significantly with renal impairment. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Hepatic Impairment

Administration of a single 450 mg dose of RELISTOR tablets in subjects with mild, moderate, and severe hepatic impairment (6 subjects each of Child-Pugh Class A, B, and C) resulted in a 1.7-, 4.8- and 3.8-fold higher C_{max} of methylnaltrexone, respectively, compared to 6 subjects with normal liver function. The $AUC_{0-\infty}$ was comparable between healthy subjects and subjects with mild hepatic impairment, but increased approximately 2.1-fold in subjects with moderate and severe hepatic impairment [*see Dosage and Administration (2.5)*].

Administration of a single dose of 0.3 mg/kg of RELISTOR injection subcutaneously in 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) did not result in any meaningful change in the AUC or C_{max} when compared to 8 healthy subjects with normal hepatic function. The effect of severe (Child-Pugh Class C) hepatic impairment on the pharmacokinetics of RELISTOR injection has not been studied [*see Dosage and Administration (2.5)*, *Use in Specific Populations (8.7)*].

Drug Interaction Studies

Effect of Methylnaltrexone and its Metabolites on CYP Enzymes:

In vitro, methylnaltrexone did not significantly inhibit or induce the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP3A4. In addition, methylnaltrexone did not induce CYP2E1.

In vitro, the methylnaltrexone metabolites, methylnaltrexone sulfate, methyl-6 α -naltrexol and methyl-6 β -naltrexol did not inhibit CYP isozymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. The metabolites of methylnaltrexone did not induce activity of CYP1A2, CYP2B6, or CYP3A4.

Effect of Methylnaltrexone and its Metabolites on Transporters

Based on the *in vitro* studies, methylnaltrexone and its three major metabolites, methylnaltrexone sulfate, methyl-6 α -naltrexol and methyl-6 β -naltrexol, are unlikely to have clinically meaningful

in vivo drug-drug interactions via inhibition of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), Multidrug Resistance Protein 2 (MRP2), Organic Anion-Transporting Polypeptide (OATP)1B1, OATP1B3, Organic Cation Transporter (OCT)1, OCT2, Organic Anion Transporter (OAT)1, OAT3, Multidrug and Toxic Extrusion Transporter (MATE)1 and MATE2-K at the recommended dosage of 450 mg orally or 12 mg subcutaneously once daily.

Methylnaltrexone: Methylnaltrexone was a substrate of OCT1, OCT2, MATE1, and MATE2-K, but not a substrate for P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1 and OAT3.

Methylnaltrexone sulfate: Methylnaltrexone sulfate was a substrate for MATE2-K and a potential substrate of BCRP, but was not a substrate of P-gp, MRP2, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and MATE1.

Methyl-6 α -naltrexol: Methyl-6 α -naltrexol was a substrate of BCRP, OCT1, OCT2, MATE1, and MATE2-K, but was not a substrate of P-gp, MRP2, OATP1B1, OATP1B3, OAT1 and OAT3.

Methyl-6 β -naltrexol: Methyl-6 β -naltrexol was a substrate of OCT1, OCT2, MATE1, and MATE2-K, but was not a substrate of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1 and OAT3.

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 intravenous infusion over 20 minutes). A single dose of methylnaltrexone bromide 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%. This change is not considered to be clinically meaningful.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year oral carcinogenicity studies have been conducted with methylnaltrexone bromide in CD-1 mice at doses up to 200 mg/kg/day (about 81 times the subcutaneous maximum recommended human dose (MRHD) of 12 mg/day based on body surface area) in males and 400 mg/kg/day (about 162 times the subcutaneous MRHD of 12 mg/day) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 243 times the subcutaneous MRHD of 12 mg/day). The 200 mg/kg/day and 400 mg/kg/day doses in male and female mice are about 2.2 and 4.4 times, respectively, the oral MRHD of 450 mg/day, and the 300 mg/kg/day dose in rats is about 6.5 times the oral MRHD of 450 mg/day, based on body surface area. Oral administration of methylnaltrexone bromide 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 subcutaneous MRHD of 12 mg/day; about 3.3 times the oral MRHD of 450 mg/day) 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 caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 micromolar concentrations, respectively). Methylnaltrexone had a hERG IC₅₀ of more than 1000 micromolar. In isolated dog Purkinje fibers, methylnaltrexone caused prolongations in action potential duration (APD). The highest tested concentration (10 micromolar) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone (up to 100 micromolar) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone concentration (100 micromolar) tested was about 186 and 373 times the human C_{max} at subcutaneous 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 or more. 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 subcutaneous dose of 0.15 mg/kg and 241 times and 66 times, respectively, the exposure at a human subcutaneous dose of 0.3 mg/kg. In conscious guinea pigs, methylnaltrexone bromide 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 subcutaneous MRHD of 12 mg/day; about 0.06 and 0.22 times, respectively, the oral MRHD of 450 mg/day). Similar adverse clinical signs were seen in adult rats at 20 mg/kg/day (about 16 times the subcutaneous MRHD of 12 mg/day; about 0.43 times the oral MRHD of 450 mg/day). 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 subcutaneous MRHD of 12 mg/day; about 0.02 and 0.11 times, respectively, the oral MRHD of 450 mg/day).

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 subcutaneous MRHD of 12 mg/day; about 1.5 times the oral MRHD of 450 mg/day). 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 subcutaneous MRHD of 12 mg/day; about 0.4 times the oral MRHD of 450 mg/day).

14 CLINICAL STUDIES

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

RELISTOR Tablets

The efficacy of RELISTOR tablets in the treatment of OIC in patients with chronic non-cancer pain was evaluated in a randomized, double-blind, placebo-controlled study (Study 1). This study compared 4-week treatment of RELISTOR tablets 450 mg orally once daily with placebo.

A total of 401 patients (200 RELISTOR, 201 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 most common pain condition requiring opioid use was back pain. Other frequently reported primary pain conditions were arthritis, neurologic/neuropathic pain, joint/extremity pain, and fibromyalgia. Prior to screening, patients were receiving opioid therapy for pain for 1 month or longer (median daily baseline oral morphine equivalent dose of 156 mg) and had OIC (less than 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 or more of oral morphine equivalents per day) a minimum of 2 weeks prior to the screening visit and received their opioid medication during the study as clinically needed. The median duration of OIC at baseline was 53 months (4 years). The mean patient age was 52 years (range 23 to 78 years), 64% were female, and 84% of patients 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 3 bisacodyl tablets taken orally once during a 24-hour period). Bisacodyl tablets were taken 5 hours or longer and up to 8 hours after study drug administration. If rescue treatment with bisacodyl tablets did not result in a bowel movement, a second dose of bisacodyl or an enema 24 hours after rescue was permitted. Enema use was permitted after rescue with bisacodyl tablets had failed at least once.

A responder analysis was performed which defined the proportion of patients with 3 or more spontaneous bowel movements (SBMs)/week, with an increase of 1 or more SBM/week over baseline, for 3 or more out of the first 4 weeks of the treatment period. A SBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours. Table 8 presents the proportion of patients who responded during the double-blind treatment period in the intent-to-treat (ITT) population, which included all randomized patients who received at least one dose of double-blind study medication.

Table 8: Proportion of Responders* in the ITT Population in Study 1 of RELISTOR Tablets for the Treatment of OIC in Patients with Chronic Non-Cancer Pain

Treatment	N	n (%)	Percent Difference ^a (2-sided 95% CI)
RELISTOR tablets 450 mg once daily	200	103 (52%)	13% (3%, 23%)
Placebo	201	77 (38%)	

CI = confidence interval; ITT = intent-to-treat;

^a Difference for active treatment vs. placebo;

*A responder is defined as a patient with 3 or more SBMs/week, with an increase of 1 or more SBM/week over baseline, for 3 or more out of the first 4 weeks of the treatment period.

RELISTOR Injection

The efficacy of RELISTOR injection in the treatment of OIC in patients with chronic non-cancer pain were evaluated in a randomized, double-blind, placebo-controlled study (Study 2). This study compared 4-week treatment of RELISTOR injection 12 mg administered subcutaneously once daily with placebo.

A total of 312 patients (150 RELISTOR, 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 or longer (median daily baseline oral morphine equivalent dose of 161 mg) and had OIC (less than 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 or more 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 OIC at baseline was 59 months (5 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.

A responder analysis was performed which defined the proportion of patients with 3 or more (SBMs) per week for each of the 4 weeks of the double-blind period. A SBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours. Table 9 presents the proportion of patients who responded 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.

Table 9: Proportion of Responders* in the mITT Population in Study 2 of RELISTOR Injection for the Treatment of OIC in Patients with Chronic Non-Cancer Pain				
Treatment	N	n (%)	Percent Difference^a (2-sided 95% CI)	P-value^b
RELISTOR injection 12 mg once daily	150	88 (59%)	20% (10%, 31%)	<0.001
Placebo	162	62 (38%)		

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

^a Difference for active treatment vs. placebo;

* A responder is defined as a patient with 3 or more SBMs per week for each of the 4 weeks in the double-blind period.

^b P-value for active treatment vs. placebo based on 2-sided Chi-square test.

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

14.2 Opioid-Induced Constipation in Adult Patients with Advanced Illness

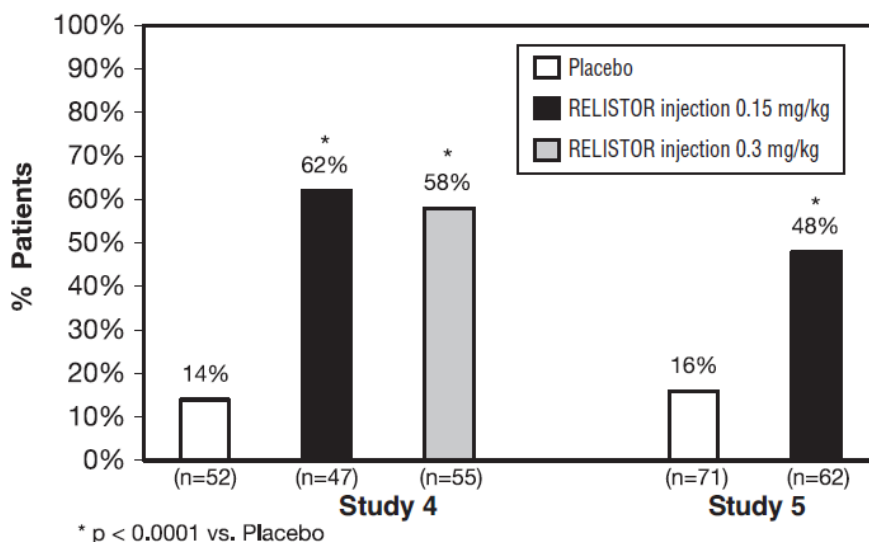
The efficacy of RELISTOR injection in the treatment of OIC in advanced illness patients receiving palliative care was demonstrated in two randomized, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21 to 100 years); 51% were females. In both studies, patients 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 of 172 mg), and had OIC (either less than 3 bowel movements in the preceding week or no bowel movement for 2 or more days). Patients were on a stable opioid regimen 3 or more 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 4 was a double-blind, placebo-controlled study which compared a single, subcutaneous dose of RELISTOR injection 0.15 mg/kg, and RELISTOR injection 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label 4-week dosing period, where RELISTOR injection could be used as needed, no more frequently than one 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 5 was a double-blind, placebo-controlled study which compared subcutaneous doses of RELISTOR injection given every other day for 2 weeks versus placebo. Patients received opioid medication for at least 2 weeks prior to receiving study medication. During the first week (Days 1, 3, 5, 7) patients received either 0.15 mg/kg RELISTOR injection or placebo. In the second week the patient's assigned dose could be increased to 0.3 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 Studies 4 and 5



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 5, 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 of RELISTOR injection was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 4, and in two open-label extension studies (Study 4 EXT and Study 5 EXT) 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 one open-label dose in Studies 4, 4 EXT, and 5 EXT, 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 RELISTOR-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 RELISTOR or placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NDC NUMBER	PACK SIZE	CONTENTS
65649-150-60	60-count bottle	85-mL bottle containing 60 tablets and 2 silica gel desiccant canisters. Each 150 mg film-coated tablet is white, round, biconvex, and debossed with “REL” on one side and plain on the other side.
65649-150-90	90-count bottle	100-mL bottle containing 90 tablets and 2 silica gel desiccant canisters. Each 150 mg film-coated tablet is white, round, biconvex, and debossed with “REL” on one side and plain on the other side.
65649-551-02	1 vial per carton	One 12 mg/0.6 mL single-dose vial containing a colorless to pale yellow solution.
65649-552-04	7 pre-filled syringes per carton	Seven 8 mg/0.4 mL single-dose pre-filled syringes with needle guard system containing a colorless to pale yellow solution.
65649-551-03	7 pre-filled syringes per carton	Seven 12 mg/0.6 mL single-dose pre-filled syringes with needle guard system containing a colorless to pale yellow solution.
65649-551-07	1 pre-filled syringe per carton	One 12 mg/0.6 mL single-dose pre-filled syringe with needle guard system containing a colorless to pale yellow solution.

Storage

Tablets

Store at up to 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Injection

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

Administration

- 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 OIC 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.
 - Inform their healthcare provider if their opioid regimen is changed, to avoid adverse reactions, such as diarrhea.

Tablets

Advise patients with chronic non-cancer pain receiving RELISTOR tablets for OIC to take RELISTOR tablets once daily with water on an empty stomach at least 30 minutes before the first meal of the day.

Injection

- Advise all patients receiving RELISTOR injection 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 *Instructions for Use*.
- Advise chronic non-cancer pain patients receiving RELISTOR injection for OIC to inject one dose every day.
- Advise patients with advanced illness receiving RELISTOR injection for OIC 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), Adverse Reactions (6.1)*].

Pregnancy

Fetal Opioid Withdrawal

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 [*see Use in Specific Populations (8.1)*].

Lactation

Advise patients that breastfeeding is not recommended during treatment with RELISTOR [*see Use in Specific Populations (8.2)*].

Manufactured for:



Salix Pharmaceuticals, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Under license from:



Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

For Injection: U.S. Patents 6,559,158; 8,247,425; 8,420,663; 8,552,025; 8,882,490; and 9,180,125

For Tablets: U.S. Patents 6,559,158; 8,420,663; 8,524,276; 8,956,651; 9,180,125; and 9,314,461

See www.salix.com for patent information. For more information, go to www.RELISTOR.com or call 1-800-321-4576.

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