Patient Instructions for Use of RELISTOR VIAL AND STANDARD SYRINGE AND NEEDLE

Introduction

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

The Patient Instructions for Use includes the following steps:

Step 1: Preparing the injection
Step 2: Preparing the syringe
Step 3: Choosing and preparing an injection site
Step 4: Injecting RELISTOR
Step 5: Disposing of supplies

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

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

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

Important Notes:

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

Step 1: Preparing the injection

1. Find a quiet place. Choose a flat, clean, well-lit working surface.

2. Wash your hands with soap and warm water before preparing for the injection.

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

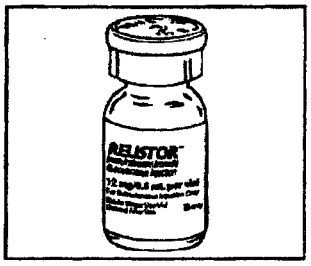

Figure 1

Step 2: Preparing the syringe

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

Figure 2

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

Figure 3

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

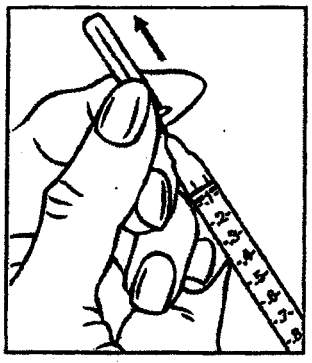

Figure 4

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

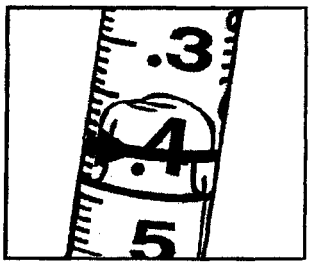

Figure 5

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

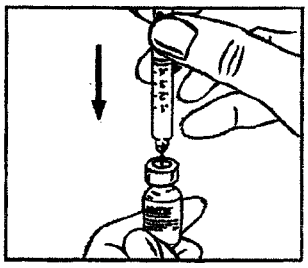

Figure 6

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

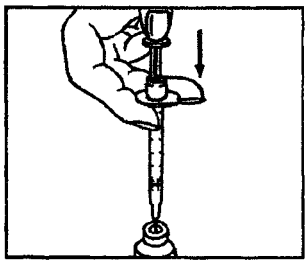

Figure 7

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

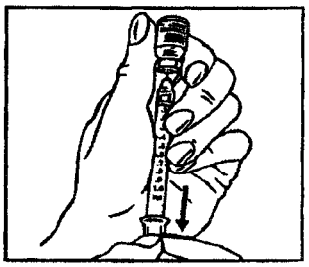

Figure 8

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

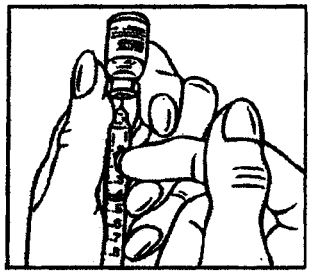

Figure 9

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

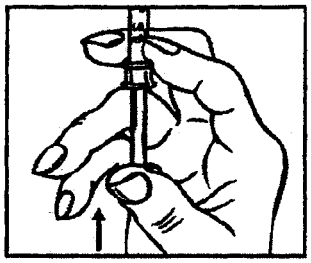

Figure 10

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

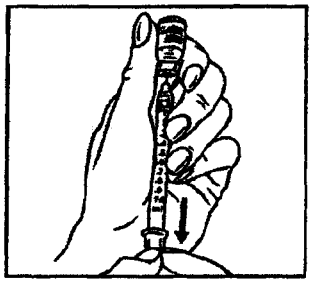

Figure 11

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

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

Step 3: Choosing and preparing an injection site

1. Choose an injection site — abdomen, thighs, or upper arms. See shaded areas in Figures 12 and 13 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 12. Abdomen or thigh – use these sites when injecting yourself or another person.

   Figure 13. Upper arm – use this site only when injecting another person.

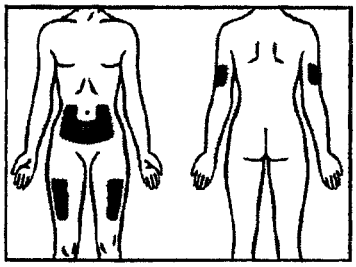

Figure12 Figure 13

2. Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (Figure 14).

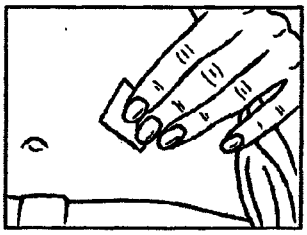

Figure 14

Step 4: Injecting RELISTOR

1. Pinch the skin around the injection site as you were instructed (Figure 15).

Figure 15

2. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (Figure 16).

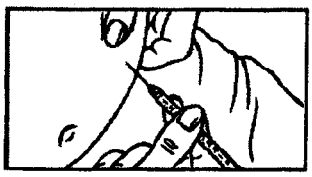

Figure 16

3. Let go of skin and slowly push down on the plunger until the syringe is empty (Figure 17).

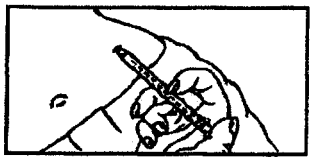

Figure 17

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

5. Hold a cotton ball or gauze over the injection site (Figure 18). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

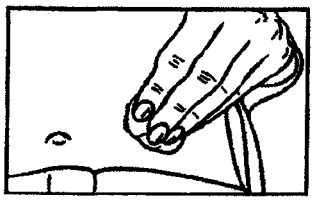

Figure 18

Step 5: Disposing of supplies

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

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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

INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. (*1*)

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial. (*3*)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician. (*5.1*)

---------- **ADVERSE REACTIONS** ----------

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

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

---------- **DRUG INTERACTIONS** ----------

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

---------- **USE IN SPECIFIC POPULATIONS** ----------

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

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

Revised: 4/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR SUBCUTANEOUS INJECTION ONLY

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

2.2 Dosing

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

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

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

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

2.3 Preparation for Injection

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

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

3 DOSAGE FORMS AND STRENGTHS

12 mg/0.6 mL solution for subcutaneous injection in a single-use vial [*see Dosage and Administration (2.2)*].

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Diarrhea

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

5.2 Peritoneal Catheters

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients with advanced illness receiving palliative care: Study 1 included a single-dose, double-blind, placebo-controlled period, whereas Study 2 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14)*]. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for 2 days). Both the methylnaltrexone bromide and placebo patients were on a stable laxative regimen for at least 3 days prior to study entry and continued on their regimen throughout the study.

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

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

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

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450 Isozymes

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

7.2 Drugs Renally Excreted

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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