1. NAME OF THE MEDICINAL PRODUCT

Relistor 12 mg /0.6 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 0.6 ml contains 12 mg methylnaltrexone bromide.
One ml of solution contains 20 mg methylnaltrexone bromide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Sterile, clear solution, colourless to pale-yellow, essentially free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.

4.2 Posology and method of administration

For adults only.

RELISTOR should be added to induce prompt bowel movements when response to usual laxative therapy has been insufficient.

The recommended dose of methylnaltrexone bromide is 8 mg (0.4 ml RELISTOR) (for patients weighing 38-61 kg) or 12 mg (0.6 ml RELISTOR) (for patients weighing 62-114 kg).

The usual administration schedule is one single dose every other day. Doses may also be given with longer intervals, as per clinical need.

Patients may receive two consecutive doses 24 hours apart, only when there has been no response (bowel movement) to the dose on the preceding day.

Patients whose weight falls outside of the ranges should be dosed at 0.15 mg/kg. The injection volume for these patients should be calculated:

Dose (ml) = patient weight (kg) x 0.0075

Renal patients
No dose adjustment is required in patients with mild or moderate impairment. In patients with severe renal impairment (creatinine clearance less than 30 ml/min), reduce the dose of methylnaltrexone bromide by one half. There are no data available from patients with end-stage renal impairment on dialysis, and RELISTOR is not recommended in these patients (see section 4.4).

Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2).

There are no data available from patients with severe hepatic impairment (Child-Pugh Class C), and RELISTOR is not recommended in these patients (see section 4.4).

Paediatric patients
There is no experience in children under the age of 18 (see section 5.2). Therefore, methylnaltrexone should not be used in the paediatric age group until further data become available.

Elderly patients
No dose adjustment is recommended based on age (see section 5.2).

Administration

RELISTOR is given as a subcutaneous injection.

It is recommended to rotate injection sites. It is not recommended to inject into areas where the skin is tender, bruised, red, or hard. Areas with scars or stretch marks should be avoided.

The three areas of the body recommended for injection of RELISTOR are upper legs, abdomen, and upper arms.

RELISTOR can be injected without regard to food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Use of methylnaltrexone bromide in patients with known or suspected mechanical gastrointestinal obstruction or acute surgical abdomen is contraindicated.

4.4 Special warnings and precautions for use

The activity of methylnaltrexone bromide has been studied in patients with constipation induced by opioids. Therefore, RELISTOR should not be used for treatment of patients with constipation not related to opioid use. If severe or persistent diarrhoea occurs during treatment, patients should be advised not to continue therapy with RELISTOR and consult their physician.

Data from clinical trials suggest treatment with methylnaltrexone bromide can result in the rapid onset (within 30 to 60 minutes on average) of a bowel movement.

Methylnaltrexone bromide treatment has not been studied in clinical trials for longer than 4 months, and should therefore only be used for a limited period (see section 5.2).

RELISTOR should only be used in patients who are receiving palliative care. It is added to usual laxative treatment.

RELISTOR is not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis (see section 4.2).

Use of methylnaltrexone bromide in patients with colostomy, peritoneal catheter, active diverticular disease or fecal impaction has not been studied. Therefore, RELISTOR should only be administered with caution in these patients.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Methylnaltrexone does not affect the pharmacokinetics of medicinal products metabolised by cytochrome P450 (CYP) isozymes. Methylnaltrexone is minimally metabolised by CYP isozymes. *In vitro* metabolism studies suggest that methylnaltrexone does not inhibit the activity of CYP1A2, CYP2E1, CYP2B6, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of the metabolism of a model CYP2D6 substrate. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.3 mg/kg of methylnaltrexone did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

The organic cation transporter (OCT)-related drug-drug interaction potential between methylnaltrexone and an OCT inhibitor was studied in 18 healthy subjects by comparing the single-dose pharmacokinetic profiles of methylnaltrexone before and

after multiple 400 mg doses of cimetidine. The renal clearance of methylnaltrexone was reduced following multiple-dose administration of cimetidine (from 31 l/h to 18 l/h). However, this resulted in a small reduction in total clearance (from 107 l/h to 95 l/h). Consequently, no meaningful change in AUC of methylnaltrexone, in addition to C_{max}, was observed before and after multiple-dose administration of cimetidine.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data with the use of methylnaltrexone bromide in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. RELISTOR should not be used during pregnancy unless clearly necessary.

Lactation
It is unknown whether methylnaltrexone bromide is excreted in human breast milk. Animal studies have shown excretion of methylnaltrexone bromide in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RELISTOR should be made, taking into account the benefit of breast-feeding to the child and the benefit of RELISTOR therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as a pure peripherally restricted opioid antagonist, the likelihood that methylnaltrexone will affect such activities is low.
Dizziness may occur, and this may have an effect on driving and use of machines (see section 4.8).

4.8 Undesirable effects

The most common drug-related adverse reactions in all patients exposed to methylnaltrexone bromide during all phases of placebo-controlled studies were abdominal pain, nausea, diarrhoea and flatulence. Generally, these reactions were mild or moderate.

The adverse reactions are classified as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), unknown (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Nervous system disorders
Common: Dizziness

Gastrointestinal disorders
Very Common: Abdominal pain, nausea, flatulence, diarrhea

Skin and subcutaneous tissue disorders
Common: Injection site reactions (e.g. stinging, burning, pain , redness, oedema), hyperhidrosis

4.9 Overdose

No case of overdose has been reported during clinical trials.

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

In the event of an overdose, signs and symptoms of orthostatic hypotension should be monitored and reported to a physician. Treatment should be initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripheral opioid receptor antagonists, ATC code: A06AH01

Mode of action
Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-receptor. *In vitro* studies have shown methylnaltrexone to be a mu-opioid receptor antagonist (inhibition constant [K_i] = 28 nM), with 8-fold less potency for kappa opioid receptors (K_i = 230 nM) and much reduced affinity for delta opioid receptors.

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 antagonist in tissues such as the gastrointestinal tract, without impacting opioid-mediated analgesic effects on the central nervous system.

Clinical efficacy and safety
The efficacy and safety of methylnaltrexone bromide in the treatment of opioid-induced constipation in patients receiving palliative care was demonstrated in two randomised, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51 % were females. In both studies, patients had advanced terminal illness and limited life expectancy, with the majority having a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients

had opioid-induced constipation defined as either <3 bowel movements in the preceding week or no bowel movement for >2 days.

Study 301 compared methylnaltrexone bromide given as a single, double-blind, subcutaneous dose of 0.15 mg/kg , or 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label, 4-week dosing period, where methylnaltrexone bromide could be used as needed, no more frequently than 1 dose in a 24-hour period. Throughout both study periods, patients maintained their usual laxative regimen. A total of 154 patients (methylnaltrexone bromide 0.15 mg/kg, n=47, methylnaltrexone bromide 0.3 mg/kg, n=55, placebo, n=52) were treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medicinal product. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62 % for 0.15 mg/kg and 58 % for 0.3 mg/kg) than placebo-treated patients (14 %); $p<0.0001$ for each dose versus placebo.

Study 302 compared double-blind, subcutaneous doses of methylnaltrexone bromide given every other day for 2 weeks versus placebo. During the first week (days 1, 3, 5, 7), patients received either methylnaltrexone bromide 0.15 mg/kg or placebo. In the second week, a patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 methylnaltrexone bromide, 71 placebo) patients were analysed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medicinal product and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of medicinal product. Methylnaltrexone bromide-treated patients had a higher rate of laxation within 4 hours of the first dose (48 %) than placebo-treated patients (16 %); $p<0.0001$. Methylnaltrexone bromide-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52 %) than did placebo-treated patients (9 %); $p<0.0001$. Stool consistency was not meaningfully improved in patients who had soft stool at baseline.

In both studies, there was no evidence to suggest differential effects of age or gender on safety or efficacy.
The effect on race could not be analysed because the study population was predominantly Caucasian (88%).

Durability of response was demonstrated in Study 302, in which the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide were also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 301, and in two open-label extension studies (301EXT and 302EXT) in which methylnaltrexone

bromide was given as needed for up to 4 months (only 8 patients up to this point). A total of 136, 21, and 82 patients received at least one open-label dose in studies 301, 301EXT, and 302EXT, respectively. RELISTOR was administered every 3.2 days (median dosing interval, with a range of 1-39 days).

The rate of laxation response was maintained throughout the extension studies for those patients who continued treatment.

There was no significant relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either methylnaltrexone bromide-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

Effect on cardiac repolarisation
In a double-blind, randomised, parallel-group ECG study of single, subcutaneous doses of methylnaltrexone bromide (0.15, 0.30 and 0.50 mg/kg), in 207 healthy volunteers, no signal of QT/QTc prolongation or any evidence of an effect on secondary ECG parameters or waveform morphology was detected as compared to placebo and a positive control (orally administered 400 mg moxifloxacin).

5.2 Pharmacokinetic properties

Absorption
Methylnaltrexone bromide is absorbed rapidly, with peak concentrations (C_{max}) achieved at approximately 0.5 hours following subcutaneous administration. The C_{max} and area under the plasma concentration-time curve (AUC) increase with dose increase from 0.15 mg/kg to 0.5 mg/kg in a dose-proportional manner. Absolute bioavailability of a 0.30 mg/kg subcutaneous dose versus a 0.30 mg/kg intravenous dose is 82 %.

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

Metabolism
Methylnaltrexone is metabolised to a modest extent in humans based on the amount of methylnaltrexone metabolites recovered from excreta. Conversion to methyl-6-naltrexol isomers and methylnaltrexone sulphate appears to be the primary pathway to metabolism. Each of the methyl-6-naltrexol isomers has somewhat less antagonist activity than parent compound, and a low exposure in plasma of approximately 8% of the drug-related materials. Methylnaltrexone sulphate is an inactive metabolite and present in plasma at a level of approximately 25 % of drug related materials. N-

demethylation of methylnaltrexone to produce naltrexone is not significant, accounting for 0.06 % of the administered dose.

Excretion
Methylnaltrexone is eliminated primarily as the unchanged active substance. Approximately half of the dose is excreted in the urine and somewhat less in faeces. The terminal disposition half-life ($t_{1/2}$) is approximately 8 hours.

Special populations

Hepatic insufficiency
The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone has not been studied.

Renal insufficiency
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. The renal clearance of methylnaltrexone decreased with increasing severity of renal impairment. Severe renal impairment decreased the renal clearance of methylnaltrexone by 8- to 9-fold; however, this resulted in only a 2-fold increase in total methylnaltrexone exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

Paediatric patients
No studies have been performed in the paediatric population (see section 4.2).

Elderly patients
In a study comparing single and multiple-dose pharmacokinetic profiles of intravenous methylnaltrexone at a dose of 24 mg between healthy, young (18 to 45 years of age n=10) and elderly (65 years of age and over n=10) subjects, the effect of age on exposure to methylnaltrexone was found to be minor. The mean steady-state C_{max} and AUC for the elderly were 545 ng/ml and 412 ng•h/ml, approximately 8.1 % and 20 %, respectively, greater than those for young subjects. Therefore, no dose adjustment is recommended based on age.

Gender
No meaningful gender differences have been observed.

Weight
An integrated analysis of pharmacokinetic data from healthy subjects indicated that methylnaltrexone mg/kg dose-adjusted exposure increased as body weight increased.

The mean methylnaltrexone exposure at 0.15 mg/kg over a weight range of 38 to 114 kg was 179 (range=139-240) ng•h/ml. This exposure for the 0.15 mg/kg dose can be achieved with a weight-band-based dose adjustment using an 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg, yielding a mean exposure of 187 (range =148-220) ng•h/ml. In addition, the analysis showed that 8 mg dose for body weight 38 to less than 62 kg and a 12 mg dose for body weight 62 to 114 kg correspond to mean doses of 0.16 (range=0.21-0.13) mg/kg and 0.16 (range=0.19-0.11) mg/kg, respectively, based on the body weight distribution of patients participating in studies 301 and 302.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Cardiac effects were observed in some non-clinical studies in canines (prolongation of action potentials in Purkinje fibers or prolongation of the QTc interval). The mechanism of this effect is unknown; however, the human cardiac potassium ion channel (hERG) appears not to be involved.

Subcutaneous injections of RELISTOR at 150 mg/kg/day decreased fertility in rats. Doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) did not affect fertility or general reproductive performance.

There was no evidence of teratogenicity in rats or rabbits. Subcutaneous injections of RELISTOR at 150/100 mg/kg/day to rats resulted in decreased offspring weights; doses up to 25 mg/kg/day (18 times the exposure [AUC] in humans at a subcutaneous dose of 0.3 mg/kg) had no effect on labour, delivery, or offspring survival and growth.

Methylnaltrexone bromide is excreted via the milk of lactating rats.

Carcinogenicity studies have not been conducted with RELISTOR.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium calcium edetate
Glycine hydrochloride
Water for injections
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
After withdrawal in the injection syringe:
Due to light sensitivity, the solution for injection should be used within 24 hours.

6.4 Special precautions for storage

Store below 30ºC.

Keep the vial in the outer carton in order to protect from light.

For storage of the medicinal product in the syringe, see section 6.3.

6.5 Nature and contents of container

Clear, Type I, flint glass, single-use vial, grey butyl rubber stopper, and aluminium overseal with flip-off-cap.

Each vial contains 0.6 ml of solution for injection.

The presentations of RELISTOR are:

1 vial of solution for injection

2 vials of solution for injection
2 sterile 1 ml injection syringes with retractable injection needle
4 alcohol swabs

7 vials of solution for injection
7 sterile 1 ml injection syringes with retractable injection needle
14 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR

This section is divided into the following subsections:

Introduction
Step 1: Setting up for an injection
Step 2: Preparing the injection syringe
Step 3: Choosing and preparing an injection site
Step 4a: Injecting RELISTOR using a pack containing injection syringe with retractable injection needle
Step 4b: Injecting RELISTOR using a standard injection syringe and injection needle
Step 5 Disposing of supplies

Introduction

The following instructions explain how to inject RELISTOR. Please read the instructions carefully and follow them step by step. You will be instructed by your healthcare professional on the techniques of self-administration. Do not attempt to administer an injection until you are sure that you understand how to give the injection. This injection should not be mixed in the same syringe with any other medicine.

You may receive either a pack containing a tray with everything needed for the injection, or a single vial only. If you receive only the vial, you will need to obtain alcohol swabs and an injection syringe.

Step 1: Setting up for an injection

1. Select a flat, clean, well-lit working surface where you can lay out the contents of your RELISTOR carton. Make sure you have set aside a proper amount of time to complete the injection.

2. Wash your hands thoroughly with soap and warm water.

3. Assemble the supplies you will need for your injection. These include the RELISTOR vial, a 1 ml injection syringe (with or without retractable needle), 2 alcohol swabs, and a cotton ball or gauze.

4. Make sure the solution in the vial is clear and colourless to pale yellow, and does not contain flakes or particles. If it is not, do not use the solution. Contact your pharmacist, nurse or physician for assistance.

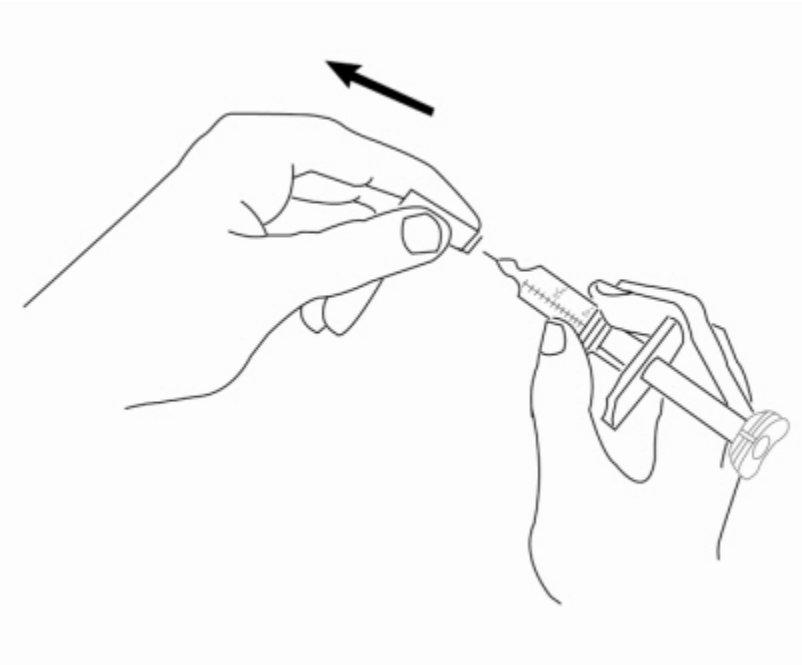
Step 2: Preparing the injection syringe

1. Remove the protective plastic cap from the vial.

2. Wipe the vial's rubber stopper with an alcohol swab and place it on your flat work surface. Make sure not to touch the rubber stopper again.

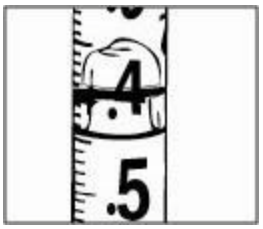
3. Pick up the syringe from your work surface. Hold the barrel of the syringe with one hand and pull the needle cover straight off. Place the needle cover back on the

work surface. DO NOT touch the needle or allow it to come in contact with any other surface.

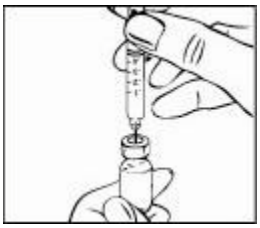


Carefully pull back the plunger on the syringe to either the 0.4 ml mark for 8 mg of RELISTOR or the 0.6 ml mark for 12 mg RELISTOR. Your healthcare professional will have advised you which dose they have prescribed for you and how often you need to take it. The usual doses are given in the table below. The dose is normally given every 48 hours (every two days) as an injection under the skin.

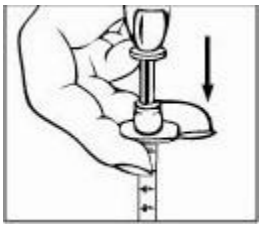
Patient weight in kg	Fill syringe to ml level (dose)
Less than 38 kg	0.15 mg/kg
38-61 kg	0.4 ml (8mg)
62-114 kg	0.6 ml (12 mg)
More than 114 kg	0.15 mg/kg



4. Insert the needle straight down into the centre of the vial stopper. Do not insert it at an angle as the needle may bend or break.. Hold the vial on the work surface with the other hand so that it can not slip off. You will feel a slight resistance as the needle passes through the stopper. Look for the needle tip inside the vial.

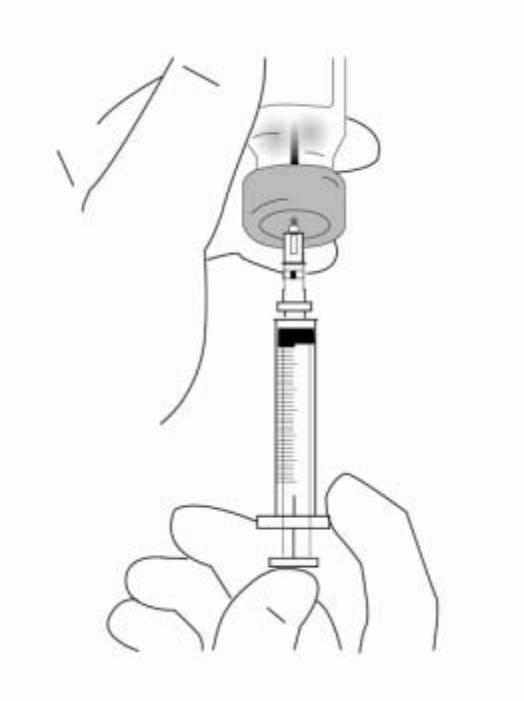


5. In order to get the air out of the syringe, gently push the plunger down to inject the air into the vial.

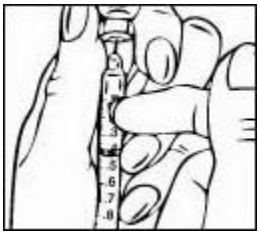


6. If you are using the supplied injection syringe with retractable injection needle, DO NOT PUSH THE PLUNGER DOWN COMPLETELY. Make sure you stop pushing the plunger when you feel resistance. If you push the plunger completely, you will hear a ‘click’ sound. This will mean that the safety mechanism has been activated, and the needle will disappear into the syringe. If this happens, discard the product and start again using another vial and syringe.

   With the needle still in the vial, turn the vial upside-down. Hold the syringe at eye level so that you can see the dosing marks and make sure the tip of the needle is in the fluid all of the time. Slowly pull the plunger down to the 0.4 ml or 0.6 ml mark on the syringe or as advised, depending on the dose prescribed by your healthcare professional. You may see some fluid or bubbles inside the vial when the syringe is properly filled. This is normal.

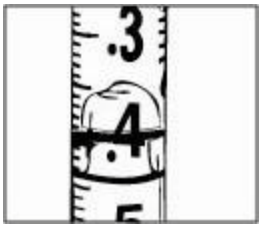


7. With the needle still inserted in the upside down vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe; be sure that you still hold onto the vial and syringe. Slowly push the plunger up until all air bubbles are removed. If you push solution back into the vial, slowly pull back the plunger to draw the correct amount of solution back into the syringe. Due to the safety design of the syringe, a small air bubble may be resistant to removal. There is no need to worry about this as it will not affect the accuracy of the dose or pose any risk to your health.

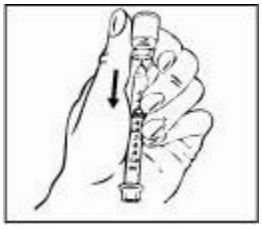


8. Always make sure you have the correct dose in the syringe. If unsure, please

contact your healthcare professional.

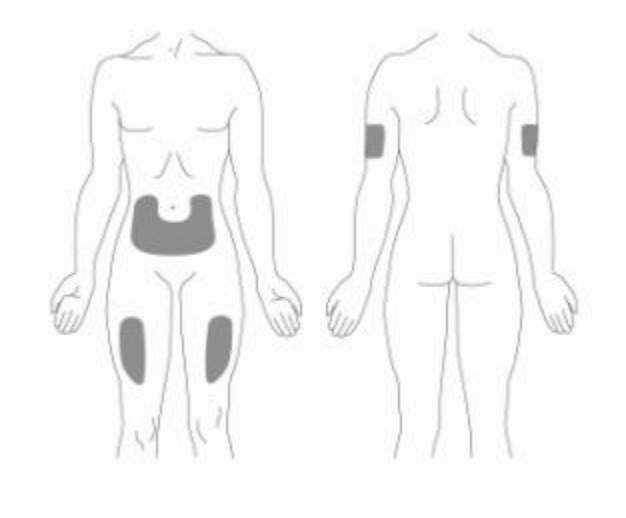


9. Remove the syringe and needle from the vial. Keep the needle attached to the syringe. Do not touch the needle or allow the needle to touch any surface.



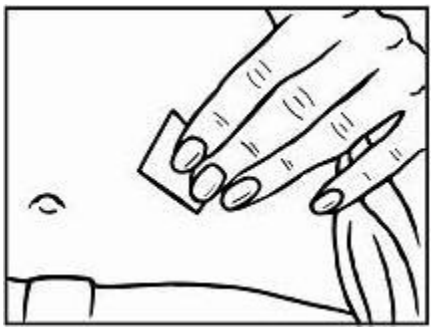
Step 3: Choosing and preparing an injection site

1. The three areas of the body recommended for injection of RELISTOR are: (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (only if injecting another person).



2. It is recommended to move to a different site each time an injection is given. Avoid repeated injections at the exact same spot previously used. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

3. To prepare the area of skin where RELISTOR is to be injected, wipe the injection site with an alcohol swab. DO NOT TOUCH THIS AREA AGAIN BEFORE GIVING THE INJECTION. Allow the injection site to air-dry before injecting.

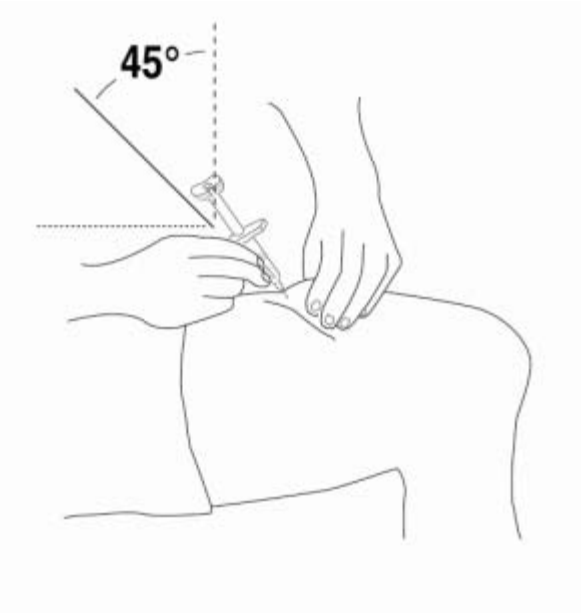


Step 4a: Injecting RELISTOR using a pack containing injection syringe with retractable injection needle

1. Holding the filled syringe with the needle pointing up, recheck the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

2. Hold the syringe in one hand like a pencil. Use the other hand to gently pinch the cleaned area of skin and hold it firmly.

3. Push the full length of the needle into the skin at a slight angle (45 degrees) with a quick, short motion.



4. After the needle is inserted, let go of the skin and slowly push the plunger all the way down until the syringe is empty and you hear a click to inject RELISTOR.

5. When you hear a click sound that means the entire contents were injected. The needle will automatically retract from the skin and be capped. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection

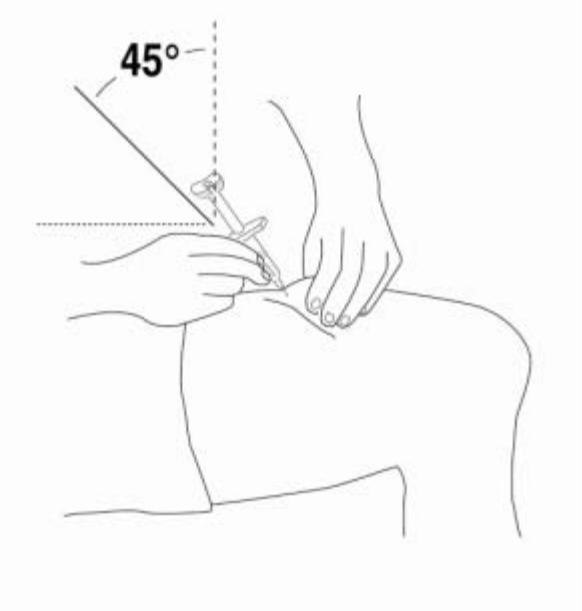
site with a plaster.

Step 4b: Injecting RELISTOR using a standard injection syringe and injection needle

1. Holding the filled syringe with the needle pointing up, recheck the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

2. Hold the syringe in one hand like a pencil. Use the other hand to gently pinch the cleaned area of skin and hold it firmly.

3. Push the full length of the needle into the skin at a slight angle (45 degrees) with a quick, short motion.



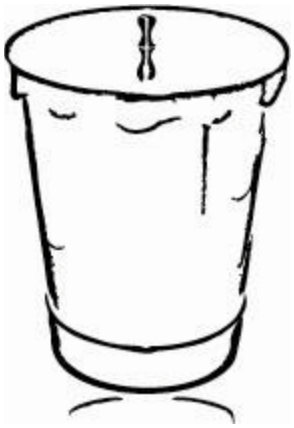
4. After the needle is inserted, let go of the skin and slowly push the plunger all the way down to inject RELISTOR.

5. When the syringe is empty, quickly pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site. Do not rub the injection site. If needed, you may cover the injection site with a plaster.

Step 5: Disposing of supplies

The capped syringe or syringe and needle should NEVER be reused. NEVER recap the needle. Dispose of the capped syringe or needle and syringe in a closable

puncture-resistant container as instructed by your doctor, nurse or pharmacist.



Frequently asked questions

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