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22nd Sept 2008

DEAR HEALTHCARE PROVIDER LETTER

Dear Healthcare Professional

The European Commission approved RELISTOR (Methylnaltrexone bromide) on 2nd July 2008, for “The treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient”. RELISTOR is administered subcutaneously.

At the request of the Regulatory Authorities, Wyeth wishes to make you aware of two important features of this new product:

1. This product is licenced for use in patients receiving palliative care, who are being treated with opioids and suffering from opioid induced constipation only. Safety and efficacy of the product has only been tested in patients with advanced illness receiving palliative care (e.g.cancer, HIV/AIDS, COPD)
2. Guidance for the proper use of the product is available in case the product is administered by the patients themselves or by their immediate caregivers (in case these are non-healthcare-professionals). To avoid overdosing, patients or caregivers should be made aware that one vial does not always contain the appropriate single dose. For patients weighing 38-61 kg only 8mg (0.4 ml) of the 12 mg (0.6 ml) dose contained in the vial should be withdrawn. The remaining volume should be discarded.

RELISTOR Presentations:

- Single vial
- 7 pack convenience kit (each pack contains one vial of RELISTOR, a single use syringe with an attached retractable needle with appropriate dose markings, and 2 alcohol swabs)
- Each pack contains a Patient Information Leaflet (PIL)

Summary of Product Characteristics

The full Summary of Product Characteristics is available at www.medicines.ie.



The Patient Information Leaflet enclosed gives “step by step” instruction to the patient on how to prepare and administer an injection of RELISTOR. Please share these instructions with patients or caregivers when explaining how to self-administer.

All individuals within your multi-disciplinary team involved in the care of these patients should be made aware of the availability of these instructions. A patient “Dosing and Administration Guide” is also enclosed in this communication.

Please contact Wyeth Medical Information Department (Phone: 01 4493500, Email: infoie@wyeth.com.) for clarification or additional information.

Regards

A handwritten signature in black ink, appearing to read "Declan O'Callaghan".

Dr. Declan O'Callaghan
Medical Director
Wyeth Pharmaceuticals Ltd.

Enclosed:

- Patient Information Leaflet
- Dosing and Administration Guide

PACKAGE LEAFLET: INFORMATION FOR THE USER

RELISTOR 12 mg/0.6 ml solution for injection Methylnaltrexone bromide

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What RELISTOR is and what it is used for
2. Before you use RELISTOR
3. How to use RELISTOR
4. Possible side effects
5. How to store RELISTOR
6. Further information

1. WHAT RELISTOR IS AND WHAT IT IS USED FOR

RELISTOR treats constipation that is caused by medicines for moderate to severe pain called opioids (for example morphine, codeine). Opioids are prescribed by your doctor. RELISTOR is given on top of your usual laxatives.

RELISTOR is for use in adults (aged 18 and over).

2. BEFORE YOU USE RELISTOR

Do not use RELISTOR

- If you are allergic (hypersensitive) to methylnaltrexone bromide or any of the other ingredients.
- If you or your doctor know that your bowels are obstructed or your bowels are in a state where there is an immediate need for surgical intervention (which has to be diagnosed by your doctor).

Take special care with RELISTOR

- If you have severe liver or kidney disease.
- If you develop severe or persistent diarrhoea (passing of frequent watery stools) discontinue therapy and contact your doctor immediately.
- It is important to be near a toilet with assistance available if necessary, since bowel movement may happen within 30 minutes after injection of the medicine.
- Please talk to your doctor if you experience persistent stomach pain, nausea, (feeling sick in the stomach) or vomiting that is new or worsened.
- Please also talk to your doctor if you have a colostomy, a peritoneal catheter, or already known disease called diverticular disease or faecal impaction.
- If you have suffered from constipation before you had to take opioids (for pain), please also talk to your doctor.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Your doctor may allow you to take other medicines, including those used for constipation.

Using RELISTOR with food and drink

RELISTOR can be taken with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

The effects of methylnaltrexone bromide in pregnant women are not known, and so the use of RELISTOR during pregnancy is not recommended.

Women using RELISTOR should not breast-feed, since it is not known if methylnaltrexone bromide passes into human breast milk.

Driving and using machines

RELISTOR may cause dizziness, and this may have an effect on driving and use of machines.

Important information about some of the ingredients of RELISTOR

This medicine contains less than 1 mmol sodium (23 mg) per dose i.e., essentially “sodium free.”

3. HOW TO USE RELISTOR

Always use RELISTOR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is 8 mg methylnaltrexone bromide (0.4 ml RELISTOR) for patients weighing 38-61 kg or 12 mg (0.6 ml RELISTOR) for patients weighing 62-114 kg. The dose is given every 48 hours (every two days) as an injection under the skin. Your doctor will determine your dose.

RELISTOR is given by an injection under the skin (by subcutaneous injection) in either (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (if not self-injecting). (See INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF RELISTOR AT THE END OF THIS LEAFLET.)

You may have a bowel movement within a few minutes to a few hours of the injection; therefore, it is recommended to have a toilet facility or bedpan near you.

If you use more RELISTOR than you should

If you have used more RELISTOR than you should (either by injecting too much on a single occasion or by using more than one injection in 24 hours), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use RELISTOR

If you forget a dose, talk to your doctor or pharmacist as soon as possible.

If you stop using RELISTOR

If you stop using RELISTOR, talk to a doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, RELISTOR can cause side effects, although not everybody gets them.

The most common side effects likely to occur in more than 1 in 10 patients:

- Abdominal pain (belly ache)
- Nausea (feeling sick in the stomach)
- Flatulence (passing wind)
- Diarrhoea (passing of frequent watery stools)

Common side effects reported in more than one in 100 patients, but in less than one in ten patients receiving RELISTOR are:

- Dizziness (light-headed)
- Reaction at the site of injection (e.g., stinging, burning, pain redness, oedema)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RELISTOR

Keep out of the reach and sight of children.

Do not use **RELISTOR** after the expiry date, which is stated on the carton and vial.

Store below 30°C.

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

Only use RELISTOR if the solution is clear, colourless to pale yellow, and does not contain flakes or particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

The syringe and needle should **NEVER** be reused. **NEVER** recap the needle. Dispose the needle and syringe as instructed by your doctor, nurse or pharmacist.

6. FURTHER INFORMATION

What RELISTOR contains

The active substance is methylnaltrexone bromide. Each vial of 0.6 ml contains 12 mg methylnaltrexone bromide. One ml of solution contains 20 mg methylnaltrexone bromide.

The other ingredients are sodium chloride, sodium calcium edetate, glycine hydrochloride, water for injections, hydrochloric acid (to adjust pH) and sodium hydroxide (to adjust pH).

What RELISTOR looks like and contents of the pack

RELISTOR is a solution for injection. It is clear, colourless to pale yellow, and does not contain flakes or particles.

Each vial contains 0.6 ml of solution.

Packs of more than one vial contain trays consisting of: one vial, one 1 ml injection syringe with retractable injection needle, and two alcohol swabs:

The following packs are available:

Single vial

Pack containing 2 vials, 2 injection syringes with retractable injection needle, and 4 alcohol swabs (i.e. 2 trays).

Pack containing 7 vials, 7 injection syringes with retractable injection needle, and 14 alcohol swabs (i.e. 7 trays).

Not all pack sizes may be marketed.

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This leaflet was last approved in 07/2008.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>. There are also links to other web sites about rare diseases and treatments.

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

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.
2. Wash your hands 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.

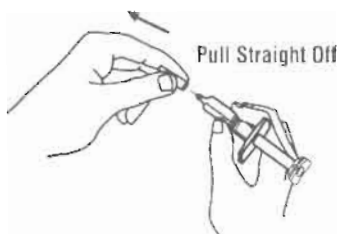
Step 2: Preparing the injection syringe

1. Remove the protective cap from the vial.



2. Wipe the vial's rubber stopper with an alcohol swab and place it on your flat work surface.

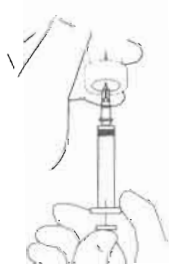
- Pick up the syringe from your work surface. Hold the barrel of the syringe with one hand and pull the needle cover straight off. Place the needle cover back on the work surface. Do not touch the needle or allow it to touch any surface. Carefully pull the syringe plunger back until the end of the plunger is at the line that represents your dose.



- 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. You will feel a slight resistance as the needle passes through the stopper. Look for the needle tip inside the vial.
- In order to get the air out of the syringe, gently push the plunger down to inject the air into the vial.

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.

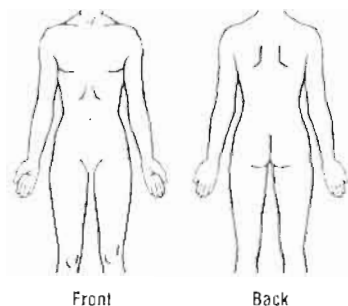
With the needle still in the vial, turn the vial upside-down. Hold the syringe at eye level and make sure the tip of the needle is in the fluid all of the time. Slowly pull the plunger down to the dosage marking on the syringe that matches your dose. You may see some fluid or bubbles inside the vial when the syringe is properly filled. This is normal.



- 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.
- 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

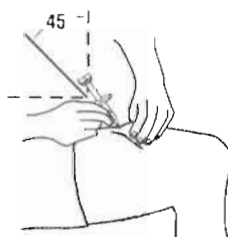
1. The three areas of the body recommended for injection of RELISTOR are: (1) your upper legs (thighs), (2) your abdomen (stomach), and (3) your upper arm (if not self injecting).



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

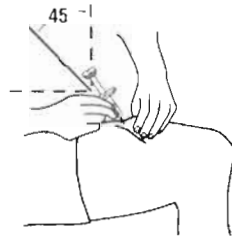
1. Holding the filled syringe with the needle pointing up, recheck the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
2. Hold the syringe 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 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 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.
6. Dispose the syringe in a closable puncture-resistant container as instructed by your healthcare professional.

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 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 bandage.