

Package leaflet: Information for the user

Signifor 0.3 mg solution for injection
Signifor 0.6 mg solution for injection
Signifor 0.9 mg solution for injection
pasireotide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Signifor is and what it is used for
2. What you need to know before you use Signifor
3. How to use Signifor
4. Possible side effects
5. How to store Signifor
6. Contents of the pack and other information

1. What Signifor is and what it is used for

Signifor is a medicine that contains the active substance pasireotide. It is used to treat Cushing's disease in adult patients for whom surgery is not an option or for whom surgery has failed.

Cushing's disease is caused by an enlargement in the pituitary gland (a gland at the base of the brain) called a pituitary adenoma. This leads the body to over-produce a hormone called adrenocorticotrophic hormone (ACTH), which in turn results in over-production of another hormone called cortisol.

The human body naturally produces a substance called somatostatin, which blocks the production of certain hormones, including ACTH. Pasireotide works in a very similar way to somatostatin. Signifor is thus able to block the production of ACTH, helping to control the over-production of cortisol and improve the symptoms of Cushing's disease.

If you have any questions about how Signifor works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use Signifor

Do not use Signifor

- if you are allergic to pasireotide or any of the other ingredients of this medicine (listed in section 6).
- if you have severe liver problems.

Warnings and precautions

Talk to your doctor before using Signifor if you currently have or have ever had:

- problems with your blood sugar levels, whether too high (as in hyperglycaemia/diabetes) or too low (hypoglycaemia);
- heart problems such as a recent heart attack, congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body) or sudden and oppressive chest pain (usually felt as pressure, heaviness, tightening, squeezing or aching across the chest);

- a heart rhythm disorder, such as an irregular heartbeat or an abnormal electrical signal called “prolongation of the QT interval”, or “QT prolongation”;
- low levels of potassium or magnesium in your blood;
- gallstones.

During your treatment with Signifor

- Signifor controls over-production of cortisol. The control may be too strong and you may experience signs or symptoms associated with a lack of cortisol, such as extreme weakness, tiredness, weight loss, nausea, vomiting or low blood pressure. If this happens, tell your doctor immediately.
- Signifor may cause your blood sugar to increase. Your doctor may want to monitor your blood sugar and start treatment with or adjust your antidiabetic medicine.
- Signifor may lower your heart rate. Your doctor may wish to monitor your heart rate using a machine that measures electrical activity of the heart (an “ECG”, or electrocardiogram). If you are using medicine to treat a heart condition, your doctor may also need to adjust its dosage.
- your doctor may also wish to check your gallbladder, liver enzymes and pituitary hormones periodically, since these might all be affected by this medicine.

Children and adolescents

Do not give this medicine to children and adolescents below 18 years old because no data are available in this age group.

Other medicines and Signifor

Signifor may affect the way some other medicines work. If you are using other medicines at the same time as Signifor (including medicines obtained without a prescription), your doctor may need to monitor your heart more carefully or change the dose of Signifor or the other medicines. Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Especially, tell your doctor if you are using:

- medicines to treat irregular heartbeat, such as medicines containing disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide, amiodarone or dronedarone;
- medicines to treat bacterial infections (by mouth: clarithromycin, moxifloxacin; via injection: erythromycin, pentamidine);
- medicines to treat fungal infections (ketoconazole, except in shampoo);
- medicines to treat certain psychiatric disorders (chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone);
- medicines to treat hay fever and other allergies (terfenadine, astemizole, mizolastine);
- medicines used in the prevention or treatment of malaria (chloroquine, halofantrine, lumefantrine);
- medicines to control blood pressure such as:
 - beta blockers (metoprolol, carteolol, propranolol, sotalol)
 - calcium channel blockers (bepridil, verapamil, diltiazem)
 - cholinesterase inhibitors (rivastigmine, physostigmine);
- medicines to control the balance of electrolytes (potassium, magnesium) in your body.

It is particularly important that you mention any of the following medicines:

- ciclosporin (used in organ transplantation to reduce the activity of the immune system);
- medicines to treat blood sugar levels that are too high (as in diabetes) or too low (hypoglycaemia), such as:
 - insulin;
 - metformin, liraglutide, vildagliptin, nateglinide (antidiabetic medicines).

Pregnancy, breast-feeding and fertility

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

- You should not use Signifor during pregnancy unless clearly necessary. If you are pregnant or think that you may be, it is important to tell your doctor who will discuss with you whether you can use Signifor during your pregnancy.
- You should not breast-feed while using Signifor. It is not known whether Signifor passes into

breast milk.

- If you are a sexually active woman, you should use an effective method of contraception during treatment. Ask your doctor about the need for contraception before taking this medicine.

Driving and using machines

Signifor may have a minor effect on the ability to drive and use machines, because some of the side effects you may experience while using Signifor, such as dizziness, headache and tiredness, may reduce your ability to drive and use machines safely.

Important information about some of the ingredients of Signifor

Signifor contains less than 1 mmol sodium (23 mg) per dose, which means it is essentially “sodium-free”.

3. How to use Signifor

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. This medicine comes in an ampoule, i.e. a small glass container.

How much Signifor to use

The recommended dose is one ampoule of Signifor 0.6 mg twice a day. Using Signifor at the same time each day will help you remember when to use your medicine. After you have started treatment, your doctor may also decide to increase your dose to one ampoule of Signifor 0.9 mg twice a day.

If side effects occur your doctor may temporarily reduce your dose by 0.3 mg per injection.

If you have liver disease before you start Signifor treatment, your doctor may want to start your treatment with a dose of one ampoule of Signifor 0.3 mg twice a day.

Ampoules of Signifor of different strengths (0.3 mg, 0.6 mg and 0.9 mg) are available to match the specific dose prescribed by your doctor.

Your doctor will check regularly how you respond to the treatment with Signifor and determine which dose is best for you.

How to use Signifor

Your doctor or nurse will instruct you on how to inject yourself with Signifor. You should also read the instructions at the end of this leaflet. If you have any questions, contact your doctor, nurse or pharmacist.

Signifor is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin. The thighs and the abdomen are good areas for subcutaneous injection. Avoid soreness and skin irritation by choosing a different site from the previous one for each injection. You should also avoid injections at sites that are sore or where the skin is irritated.

Do not use Signifor if you notice the solution is not clear or contains particles. The solution should be free of visible particles, clear and colourless.

How long to use Signifor

You should continue using Signifor for as long as your doctor tells you to.

If you use more Signifor than you should

If you accidentally use more Signifor than your doctor prescribed, immediately contact your doctor, nurse or pharmacist.

If you forget to use Signifor

Do not inject a double dose of Signifor to make up for a forgotten dose. If you forgot to inject a dose

of Signifor, simply inject the next dose at the scheduled time.

If you stop using Signifor

If you interrupt your treatment with Signifor your cortisol level may increase again and your symptoms may come back. Therefore, do not stop using Signifor unless your doctor tells you to.

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

4. Possible side effects

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

Some side effects may be serious. Tell your doctor straight away if you get any of the following:

Very common (may affect more than 1 in 10 people)

- Changed level of sugar in the blood. You may experience excessive thirst, high urine output, increased appetite with weight loss, tiredness, nausea, vomiting, abdominal pain.
- Gallstones or associated complications. You may experience fever, chills, yellowing of skin/eyes, sudden back pain or pain in the right side of your abdomen.
- Extreme tiredness.

Common (may affect up to 1 in 10 people)

- Low cortisol levels. You may experience extreme weakness, tiredness, weight loss, nausea, vomiting and low blood pressure.
- Slow heart beat.
- Low blood pressure. You may experience dizziness, light headedness and dizziness or fainting on standing up.
- Problems with bile flow (cholestasis). You may experience yellowing of the skin, dark urine, pale stools and itching.
- Inflammation of the gallbladder (cholecystitis).

Other side effects of Signifor may include:

Very common (may affect more than 1 in 10 people)

- Diarrhoea
- Nausea
- Stomach pain
- Pain at the injection site

Common (may affect up to 1 in 10 people)

- Prolonged QT interval (an abnormal electrical signal in your heart that can be seen in tests)
- Loss of appetite
- Vomiting
- Headache
- Dizziness
- Hair loss
- Itching (pruritus)
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Abnormal results of liver function tests
- Abnormal results of pancreatic function tests
- Abnormal blood coagulation properties

Uncommon (may affect up to 1 in 100 people)

- Low level of red blood cells (anaemia)

Not known (frequency cannot be estimated from the available data)

- Increased levels of ketone bodies (a group of substances produced in the liver) in your urine or blood (diabetic ketoacidosis) as a complication of an increased level of sugar in your blood. You may experience fruity scented breath, trouble breathing and confusion.
- Oily or fatty stools
- Discoloured stools

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Signifor

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the ampoule label and carton after “EXP”. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Signifor contains

- The active substance is pasireotide.
Signifor 0.3 mg: One ampoule of 1 ml solution contains 0.3 mg pasireotide (as pasireotide diaspertate).
Signifor 0.6 mg: One ampoule of 1 ml solution contains 0.6 mg pasireotide (as pasireotide diaspertate).
Signifor 0.9 mg: One ampoule of 1 ml solution contains 0.9 mg pasireotide (as pasireotide diaspertate).
- The other ingredients are mannitol, tartaric acid, sodium hydroxide and water for injections.

What Signifor looks like and contents of the pack

Signifor solution for injection is a clear, colourless solution in an ampoule. Each ampoule contains 1 ml of solution for injection.

Signifor is available in packs containing 6 ampoules or in multipacks containing 18 (3 packs of 6), 30 (5 packs of 6) or 60 (10 packs of 6) ampoules.

Not all strengths or pack sizes may be marketed in your country.

Marketing Authorisation Holder and Manufacturer

Recordati Rare Diseases
Tour Hekla
52 avenue du Général de Gaulle
92800 Puteaux
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder

United Kingdom

Recordati Rare Diseases UK Ltd.

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INSTRUCTIONS FOR USE OF SIGNIFOR SOLUTION FOR INJECTION

This medicine comes in an ampoule, i.e. a small glass container. Signifor should be administered using sterile disposable syringes and injection needles.

Your doctor or nurse will have instructed you on how to use Signifor ampoules. However, before using the ampoule, please read the following information carefully. If you are not sure about giving yourself the injection or if you have any questions, please ask your doctor or nurse for help.

The injection can be prepared using either two different needles to draw up and inject the solution or one short fine injection needle for both steps. Based on the local clinical practice, your doctor or nurse will tell you which method to use. Please follow their instructions.

Store Signifor ampoules according to the storage conditions listed on the box.

Important safety information

Caution: Keep the ampoules out of the reach of children.

What do I need

To give yourself an injection you will need:

1. One Signifor ampoule
2. Alcohol wipes or similar
3. One sterile syringe
4. One long thick blunt sterile needle for drawing up the solution (your doctor or nurse will tell you if this is needed)
5. One short fine sterile needle
6. A sharps container or other rigid closed disposal container

The injection site

The injection site is the place on your body where you are going to give yourself the injection. Signifor is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin. The thighs and the abdomen are good areas for subcutaneous injection. Avoid soreness and skin irritation by choosing a different site from the previous one for each injection. You should also avoid injections at sites that are sore or where the skin is irritated.

Getting started

When you are ready to give yourself the injection, carefully follow the steps below:

- Wash your hands thoroughly with soap and water.
- Use new disposable needles and syringes every time you give yourself an injection. Use syringes and needles only once. **Never** share needles and syringes.
- Take the ampoule out of the box.
- Inspect the ampoule. **DO NOT USE** if it is broken or if the liquid looks cloudy or contains particles. In all these cases, return the entire pack to the pharmacy.

To reduce local discomfort, it is recommended that the solution is at room temperature before administration.

Ampoules should be opened just prior to administration, and any unused portion discarded.

Check the expiry date and the dose

Check the expiry date which is stated on the ampoule label (after “EXP”) and check that the ampoule contains the dose that your doctor has prescribed.

DO NOT USE if the medicine has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

How to inject Signifor



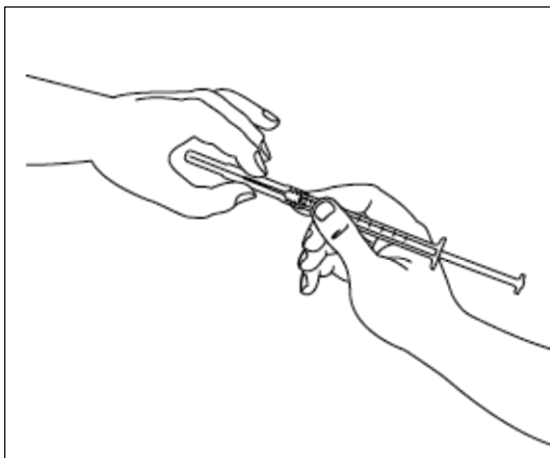
Step 1:

Signifor solution for injection is filled in a break-off ampoule. The coloured dot on the top part marks the position of the breaking point on the neck of the ampoule. Tap the ampoule with your finger in order to make sure there is no liquid in the top part when you open the ampoule.



Step 2:

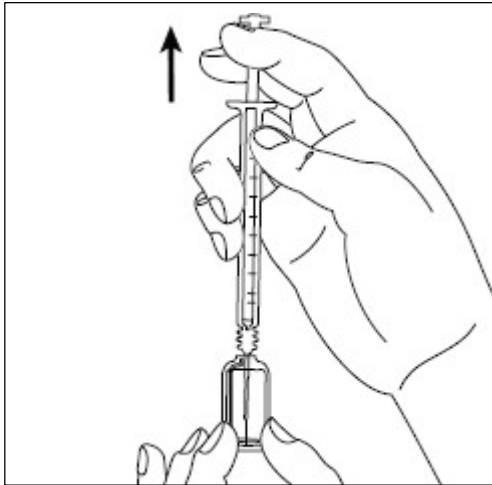
Recommended procedure: hold the ampoule in an upright position with the coloured dot facing away from you. Hold the base of the ampoule in one hand. Keeping your thumbs together above and below the neck, break off the top of the ampoule at the breaking point. Once the ampoule is open, put it upright on a clean, flat surface.



Step 3:

Take the sterile syringe and attach the needle to it. If you have been told to use two needles, you should use the long thick blunt one for this step.

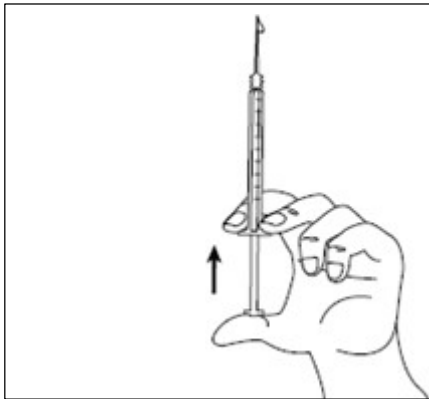
Before you proceed to step 4, clean the injection site with an alcohol wipe.



Step 4:

Remove the cover from the needle. Put the needle into the ampoule and pull the plunger to draw up the entire contents of the ampoule into the syringe.

If you have been told to use two needles, you should now replace the long needle with the short one.

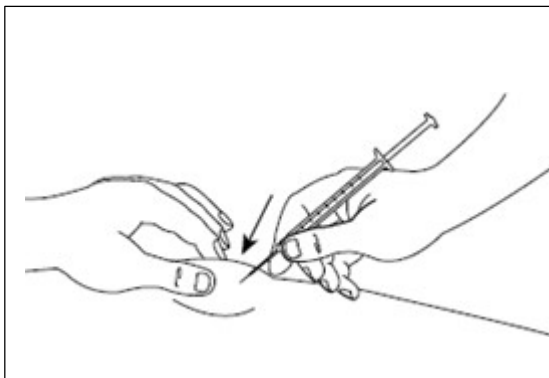


Step 5:

Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger. Tap the syringe with your fingers to get rid of air bubbles.

Make sure there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.

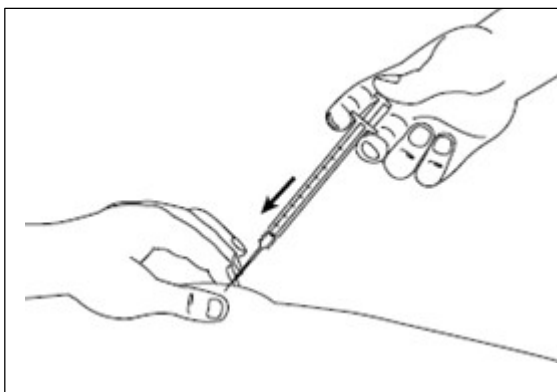
Do not let the needle touch anything. You are now ready to inject.



Step 6:

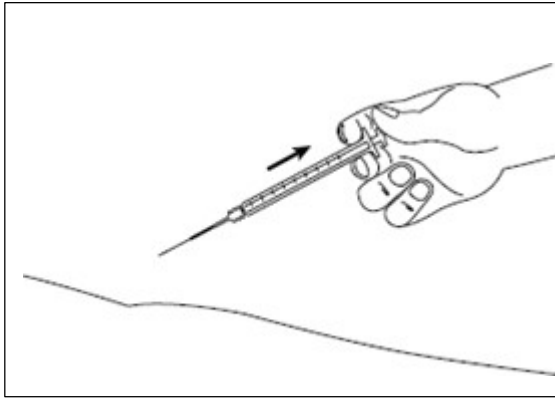
Gently pinch the skin at the injection site and, holding the needle at an angle of approximately 45 degrees (as shown in the picture) insert it into the injection site.

Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, first remove the needle from the skin, then replace the short needle with a new one and insert it into a different injection site.



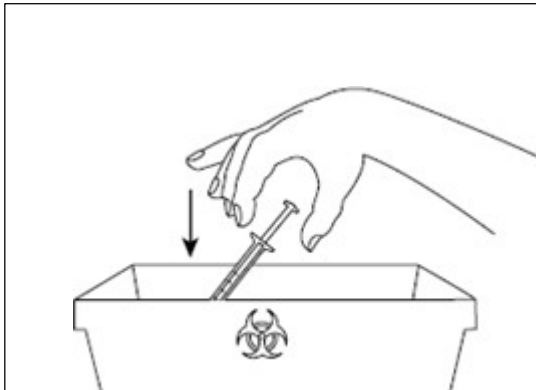
Step 7:

Always keeping your skin pinched, slowly press the plunger down as far as it will go until all the solution is injected. Keep the plunger pressed down and hold the syringe in place for 5 seconds.



Step 8:

Slowly release the skin fold and gently pull the needle out. Put the cover back on the needle.



Step 9:

Dispose of the used syringe and needle immediately in a sharps container or other rigid closed disposal container. Any unused product or waste material should be disposed of in accordance with local requirements.