

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS**  
**(PREPARATIONS) - 1986**

The medicine is dispensed with a doctor's prescription only

**Signifor® 0.3 mg/1 ml**  
**Solution for injection**

**Active ingredient**

Each ampoule contains:

0.3 mg pasireotide (as pasireotide diaspertate)

**Signifor® 0.6 mg/1 ml**  
**Solution for injection**

**Active ingredient**

Each ampoule contains:

0.6 mg pasireotide (as pasireotide diaspertate)

**Signifor® 0.9 mg/1 ml**  
**Solution for injection**

**Active ingredient**

Each ampoule contains:

0.9 mg pasireotide (as pasireotide diaspertate)

**Inactive ingredients and allergens:** See section 6 'Further information'. Also see "Important information about some of the ingredients of the medicine" section.

**Read the leaflet carefully in its entirety before using the medicine.** This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

**1. WHAT IS THE MEDICINE INTENDED FOR?**

The medicine is used to treat adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

**Therapeutic group:**

Pasireotide is a synthetic compound derived from somatostatin.

The medicine belongs to the group of somatostatin analogs.

Cushing's disease is caused by an enlargement in the pituitary gland (a gland at the base of the brain) called a benign pituitary tumor (adenoma). This condition leads the body to over-produce a hormone called adrenocorticotrophic hormone (ACTH), which leads to the 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 similar way to the way somatostatin works. Signifor is thus able to block the production of ACTH, and thereby help control the over-production of cortisol and improve the symptoms of Cushing's disease.

**2. BEFORE USING THE MEDICINE**

**X Do not use the medicine if:**

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

## **! Special warnings regarding use of the medicine**

**Before treatment with Signifor, tell your doctor if you currently have, or have ever had in the past:**

- problems with your blood sugar levels, whether too high (as in hyperglycemia/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 a sensation of pressure, heaviness, tightening, squeezing or aching across the chest).
- a heart rhythm disorder, such as an irregular or too low 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.
- kidney problems.

## **During 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 the doctor immediately.

## **Children and adolescents**

Do not give this medicine to children and adolescents below the age of 18 as no data are available regarding the safety and efficacy of use of this preparation in children and adolescents.

## **Tests and follow-up**

- Signifor may cause your blood sugar level to increase. Your doctor may want to monitor your blood sugar levels and start treatment with/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 heart problems, 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 be affected by the medicine.

## **Drug interactions**

**If you are taking, or have recently taken, or if you may take other medicines, including non-prescription medicines, nutritional supplements and vaccines, tell the doctor or pharmacist.**

Signifor may affect the way other medicines work. If you are taking other medicines at the same time that you are taking Signifor (including non-prescription medicines), your doctor may need to monitor your heart activity more carefully or change the dose of Signifor or the other medicines.

Especially inform your doctor if you are taking any of the following medicines:

- medicines to treat irregular heartbeat, such as medicines containing disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide, amiodarone or dronedarone;
- medicines to treat bacterial infections (given by mouth: clarithromycin, moxifloxacin; given by 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 the following medicines:

- cyclosporin (used in organ transplantation to reduce the activity of the immune system);
- medicines used 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**

Consult with your doctor or pharmacist before using any medicine.

- You should not use Signifor during pregnancy unless its use is clearly necessary. If you are pregnant or think that you may be pregnant, it is important to inform your doctor who will discuss with you whether you can take Signifor during your pregnancy.
- Do not breast-feed during the course of treatment with 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 the medicine.

### **Driving and using machines**

Signifor may have a minor effect on the ability to drive and use machines, since 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 the medicine**

Signifor contains less than 1 mmol sodium (23 mg) per dose; it is therefore considered essentially sodium-free.

## **3. HOW SHOULD YOU USE THE MEDICINE?**

Always use the preparation according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

The medicine is supplied in an ampoule, i.e. a small glass container.

### **How much Signifor to use**

The dosage and the treatment regimen will be determined by the doctor only. The recommended dose is usually 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 had liver disease before starting Signifor treatment, your doctor may want to start your treatment with a dose of one ampoule of Signifor 0.3 mg twice a day.

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

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

### **Do not exceed the recommended dose.**

### **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, refer to your doctor, nurse or pharmacist.

Signifor is intended for subcutaneous use. This means that the preparation is injected through a short needle into the fatty tissue just under the skin. The thighs and the abdomen are good areas for subcutaneous

injections. Avoid soreness and skin irritation by choosing a different site from the previous one for each injection. You should also avoid injections in painful areas 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 colorless.

### **Duration of Signifor treatment**

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

**If you accidentally take a higher dosage** than the dosage your doctor prescribed for you, immediately refer to your doctor or pharmacist.

If you accidentally took an overdose or if a child accidentally took the medicine, refer immediately to the doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

### **If you forgot 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, inject the next dose at the scheduled time.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor or pharmacist.

### **If you stop the treatment with Signifor**

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

**Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.**

**If you have any further questions regarding use of the medicine, consult your doctor or pharmacist.**

## **4. SIDE EFFECTS**

As with any medicine, use of Signifor may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

**Some side effects can be serious. Tell your doctor straight away if you experience any of the following symptoms:**

Very common side effects (effects which appear in more than 1 of 10 users):

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

Common side effects (effects which appear in 1-10 of 100 users):

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

**Additional side effects:**

Very common side effects (effects which appear in more than 1 of 10 users):

- Diarrhea.
- Nausea.
- Abdominal pain.
- Pain at the injection site.
- High level of glycated hemoglobin in the blood (a test that indicates the average blood sugar level in the past few months).

Common side effects (effects which appear in 1-10 of 100 users):

- Prolonged QT interval (an unwanted effect on the electrical activity of the heart that can be seen in tests).
- Loss of appetite.
- Vomiting.
- Headache.
- Dizziness.
- Hair loss.
- Itching (pruritus).
- Muscle pain.
- Joint pain.
- Abnormal results of liver function tests.
- Abnormal results of pancreatic function tests.
- Abnormal blood coagulation properties.

Uncommon side effects (effects which appear in 1-10 of 1,000 users):

- Low level of red blood cells (anemia).

Side effects of unknown frequency (effects whose frequency has not yet been determined):

- 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.

**If a side effect occurred, if any of the side effects worsen or if you experience a side effect not mentioned in the leaflet, consult your doctor.**

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage ([www.health.gov.il](http://www.health.gov.il)) that directs you to the online form for reporting side effects, or by entering the link: <https://sideeffects.health.gov.il>

**5. HOW TO STORE THE MEDICINE?**

- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without explicit instructions from the doctor.
- Do not use the medicine after the expiry date (exp. date) which appears on the ampoule label and carton. The expiry date refers to the last day of that month.

**Storage conditions**

- Do not store above 30°C.
- Store in the original package in order to protect from light.
- 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 colorless.
- Do not throw away 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. **FURTHER INFORMATION**

- In addition to the active ingredient the medicine also contains: Mannitol, tartaric acid, sodium hydroxide and water for injection.
- What the medicine looks like and the contents of the pack:  
Signifor solution for injection is a clear, colorless solution in an ampoule. Each ampoule contains 1 ml of solution for injection.  
Signifor is marketed in packs containing 30 ampoules (5 packs of 6) or 60 ampoules (10 packs of 6).  
Not all pack sizes may be marketed.
- **Registration Holder and its address:** Medison Pharma Ltd., 10 Hashiloach St., Petach Tikva.
- **Name and address of the manufacturer:** Novartis Pharma Stein AG, Stein, Switzerland, for Recordati Rare Diseases, Puteaux, France.

This leaflet was revised in December 2021 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Signifor 0.3 mg/1 ml solution for injection: 150 59 33762

Signifor 0.6 mg/1 ml solution for injection: 150 60 33767

Signifor 0.9 mg/1 ml solution for injection: 150 61 33768

### **Instructions for use of Signifor**

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 instruct 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 refer to your doctor or nurse for help.

The injection can be prepared using either two different needles to draw up and inject the solution or by using 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**

**In order 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 injection. This means that the medicine 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 with someone else.
- Take the ampoule out of the box.
- Inspect the ampoule carefully. **Do not use** the ampoule if it is broken or if the liquid looks cloudy or contains particles. In all such cases, return the entire pack to the pharmacy.



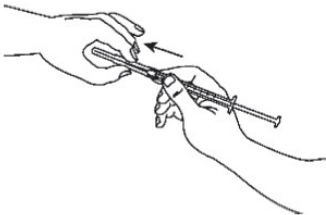

To reduce local discomfort, it is recommended that the solution be at room temperature before administration. Ampoules should be opened just prior to administration, and any unused remnants discarded.

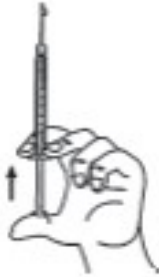



### Check the expiry date and the dosage

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

**Do not use if the expiry date of the medicine has passed, or if the dosage is incorrect. In both these cases, return the entire pack to the pharmacy.**

### How to inject Signifor

<p><b>Step 1:</b> Signifor solution for injection is stored in a break-off ampoule. The colored 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.</p>	
<p><b>Step 2:</b> Recommended procedure: hold the ampoule in an upright position with the colored 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, place it upright on a clean, flat surface.</p>	
<p><b>Step 3:</b> 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.</p>	
<p><b>Step 4:</b> Remove the cover from the needle. Insert 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.</p>	

<p><b>Step 5:</b> Hold the syringe facing upwards 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 are no air bubbles in the syringe by pressing the plunger until the first drop appears at the tip of the needle.  Do not let the needle come into contact with anything. You are now ready to inject.</p>	
<p><b>Step 6:</b> 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.</p>	
<p><b>Step 7:</b> Always keeping your skin pinched, slowly press the plunger down as far as it will go <u>until all the solution is injected</u>. Keep the plunger pressed down and hold the syringe in place for 5 seconds.</p>	
<p><b>Step 8:</b> Slowly release the skin fold and gently pull the needle out. Put the cover back on the needle.</p>	
<p><b>Step 9:</b> Dispose of the used syringe and needle immediately into a container intended for sharp items or another rigid closed disposal container. Any unused product or waste material should be disposed of in accordance with local requirements.</p>	