

PART III: CONSUMER INFORMATION**PrSIGNIFOR®
(Pasireotide injection)**

This leaflet is part III of a three-part "Product Monograph" published when SIGNIFOR® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SIGNIFOR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is:**

SIGNIFOR 0.3 mg, 0.6 mg and 0.9 mg solution for injection contains the active substance pasireotide, which is a synthetic compound derived from somatostatin.

What the medication is used for:

SIGNIFOR (pasireotide) is used in adults. It is a medicine to treat a disease called Cushing's. It is used when surgery is not an option or has not produced the required results. Cushing's disease is a condition caused by an enlargement of a part of the gland called the pituitary at the base of the brain, a so-called pituitary adenoma. This adenoma leads the body to make large amounts of a hormone called adrenocorticotrophic hormone (ACTH).

SIGNIFOR should only be prescribed and supervised by a qualified doctor. To receive SIGNIFOR, you must be enrolled in the Access Program for SIGNIFOR.

What it does:

SIGNIFOR is a medicine containing a novel synthetic substance that mimics the action of somatostatin, a substance normally found in the human body, which can block the production of certain hormones, such as ACTH.

When it should not be used:

- If you are allergic to pasireotide or to any other ingredient in the medication or its container
- If you have moderate or severe liver problems
- If you have uncontrolled diabetes
- If you are pregnant
- If you are a woman of childbearing potential and not using contraception (birth control)
- If you are breastfeeding
- If you have heart problems

What the medicinal ingredient is:

Pasireotide diaspertate.

What the nonmedicinal ingredients are:

Mannitol, sodium hydroxide, tartaric acid, and water for injections.

What dosage forms it comes in:

SIGNIFOR is a solution supplied in an ampoule containing 1 mL of a clear, colourless solution.

Each ampoule contains 0.3 mg or 0.6 mg or 0.9 mg pasireotide (as pasireotide diaspertate).

SIGNIFOR is available in packs containing 60 ampoules.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

Serious side effects include:

- Liver problems
- Heart problems (i.e. slow or irregular heart beat)
- Changes in blood glucose levels

BEFORE you use SIGNIFOR talk to your doctor or pharmacist if:

- You have problems with your blood sugar levels, either too high (hyperglycemia/diabetes) or too low (hypoglycaemia)
- You have problems with your liver
- You have severe kidney problems
- You have heart problems. This includes an abnormal heart rate or rhythm. This can also include problems with the electrical system of your heart called QT prolongation
- Take medicines to control your heart beat (antiarrhythmics) or medicines that may have an unwanted effect on the function of the heart beat (QT prolongation)
- You have a history of fainting spells
- You have low levels of pituitary hormones
- You have low levels of potassium or magnesium in your blood
- You have conditions such as vomiting, diarrhea, dehydration
- You have gallstones
- You are pregnant, may be pregnant or thinking or becoming pregnant. Your doctor will discuss whether you can become pregnant or not.
- You are breastfeeding. It is not known if SIGNIFOR passes into breast milk
- You take medicines to control your blood pressure (such as beta-blockers or calcium channel blockers)
- You take medicines to control electrolytes (potassium, magnesium) balance in your body
- You take medicines that affect how your blood clots

Your doctor may wish to check your blood sugar levels. You may need to start taking medicines to control your blood sugar levels or your doctor may adjust the medicines you are now taking to control your blood sugar levels.

Before your doctor prescribes SIGNIFOR, they should do tests including:

- Blood tests
- Liver tests
- Electrocardiogram, to measure the electrical activity of the heart

- Gallbladder ultrasound

These tests should be repeated during treatment.

Your doctor may wish to check your gallbladder, liver enzymes and pituitary hormones on a regular basis.

During your treatment with SIGNIFOR

Tell your doctor straight away if:

- You are feeling very weak
- You lose weight
- You have nausea or vomiting
- You have low blood pressure

Children and adolescents (under 18 years old)

SIGNIFOR is not to be used in children or adolescents.

To prevent pregnancy, female patients of childbearing potential should use adequate birth control.

Driving and Using Machines: Before you perform tasks which may require special attention, wait until you know how you respond to SIGNIFOR as fatigue or headache can occur.

INTERACTIONS WITH THIS MEDICATION

The following list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems while receiving SIGNIFOR. You should check with your doctor or pharmacist before taking any other medication with SIGNIFOR.

Drugs that may interact with SIGNIFOR include:

- Anti-arrhythmics used to treat irregular heart beat such as amiodarone, disopyramide, procainamide, quinidine, sotalol, ibutilide, dronedarone, flecainide, propafenone
- Medicines that may have an unwanted effect on the function of the heart (QT prolongation) such as:
 - antipsychotics (e.g., haloperidol, pimozide, droperidol, ziprasidone, chlorpromazine)
 - antidepressants (e.g., imipramine, citalopram, amitriptyline, maprotiline, venlafaxine)
 - methadone
 - antibiotics (e.g., clarithromycin, moxifloxacin, erythromycin, azithromycin, tacrolimus, levofloxacin, ciprofloxacin)
 - antimalarials (e.g., chloroquine, quinine)
 - antifungals (e.g., ketoconazole, fluconazole, voriconazole)
 - dopamine receptor antagonists (e.g. domperidone)
 - antiemetics (e.g., intravenous ondansetron)
 - cancer drugs (e.g., sunitinib, nilotinib, vandetanib, lapatinib, vorinostat)
- Asthma drugs (e.g., formoterol, salmeterol)
- Diuretics (water pills)
- Laxatives and enemas
- Amphotericin B
- High dose corticosteroids
- Medicines that decrease heart rate and prolong the PR interval:
 - antihypertensives (e.g., atenolol, diltiazem, verapamil, clonidine)
 - drugs to treat heart failure (e.g., digoxin)

- drugs to treat multiple sclerosis (e.g., fingolimod)
- drugs to treat HIV infection (e.g., atazanavir)
- Certain other medicines, such as cyclosporine, bromocriptine
- Medicines that work to prevent blood clots (anticoagulants)
- Antidiabetic drugs including insulin and oral medicines

This list includes some, but not all, of the drugs that may increase the risk of side effects while receiving SIGNIFOR. Tell your doctor or pharmacist if you are taking these or any other medicines even those not prescribed (including any over the counter drugs, vitamins, or herbal medicines).

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of SIGNIFOR is 0.6 mg injected under your skin (subcutaneous) two times a day (approximately every 12 hours). Using SIGNIFOR at the same time each day will help you remember when to use your medicine.

Your doctor will monitor how you respond to the treatment with SIGNIFOR and may ask you to change to a higher or lower dose.

How long to take SIGNIFOR

Your doctor will regularly check your condition to see if the treatment is working. You will need to take SIGNIFOR for as long as your doctor tells you. This is a long-term treatment, possibly lasting for years. If you stop your treatment your symptoms may come back.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Do not use a double dose of SIGNIFOR to make up for a forgotten dose. If you forgot to administer a dose of SIGNIFOR simply take your next injection at the scheduled time.

Instructions for use of SIGNIFOR

Your health care practitioner 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 how to give the injection or you have any questions, please ask your doctor, nurse or pharmacist 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 the SIGNIFOR ampoules according to the storage condition listed on the box.

Important Safety Information

Caution: Keep the ampoule out of the reach of children

What you need, to give yourself a subcutaneous injection:

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 injections. 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 or 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.
- Always 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.
- Carefully 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 product pack to the pharmacy.

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



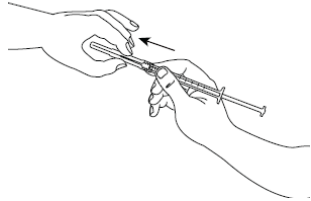
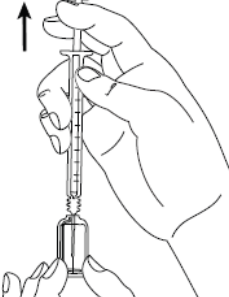
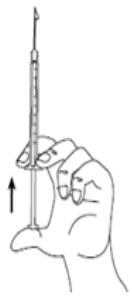
Check the expiry date and the dose:


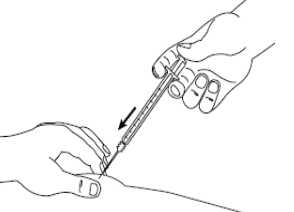
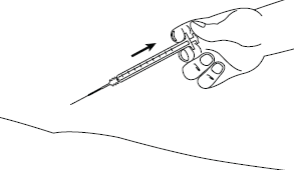
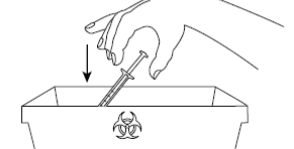
Check the expiry date (EXP) which is stated on the ampoule label and check that it is the dose your doctor has prescribed for you.

DO NOT USE if the product has expired or if the dose is not the one you have been prescribed. In both cases, return the entire product pack to the pharmacy.

How to inject SIGNIFOR

	<p>Step 1: SIGNIFOR solution for injection is filled in a break-off ampoule. The colored dot on the top part marks the position of the breaking cut 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>
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	<p>The solution should be free of visible particles, clear and colorless. Do not use SIGNIFOR if the solution is not clear or contains particles.</p>
	<p>Step 2: 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 cut. Once open, put the ampoule upright on a clean, flat surface.</p>
	<p>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.</p> <p>Before you proceed to step 4, clean the injection site with an alcohol wipe.</p>
	<p>Step 4: Remove the cover from the needle. Put the needle into the ampoule and pull the plunger to draw 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>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.</p> <p>Do not let the needle touch anything. You are now ready to inject.</p>
	<p>Step 6: Gently pinch the skin at the injection site and, holding the needle at an angle of approximately 45 degrees (as</p>

	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 down the plunger 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.
	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 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Diarrhea, nausea, abdominal pain, vomiting, loss of appetite, constipation, indigestion, bloating, weight loss, altered taste, flatulence, dry mouth
- Fatigue, weakness, discomfort, muscle and joint pain, drowsiness, fainting, dizziness, tremor
- Local pain, redness, irritation, itching, rash, hives and/or swelling at the injection site
- Dry, itchy, sweaty, bruised skin
- Headache
- Hair loss
- Blurred vision
- Flushing

If any of these affects you severely or does not go away, tell your doctor.

SIGNIFOR can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
High level of sugar in the blood excessive thirst, high urine output, increased appetite with weight loss, tiredness, nausea, vomiting, abdominal pain			√
Gallstones or complications - right-sided chest pain below rib cage -pain in the back right shoulder blade - nausea, vomiting, gas, burping - fever with chills, abdominal pain, or yellowing of skin/eye			√
Common			
Low cortisol levels extreme weakness, weight loss, nausea, vomiting, low blood pressure			√
Adrenal Insufficiency Fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain		√	
Heartbeat disturbance weakness, tiredness, shortness of breath, lightheadedness, fainting, dizziness, palpitations, seizures			√
Prolonged QT interval dizziness, palpitations, fainting, seizures			√
Low blood pressure Dizziness, fainting, lightheadedness		√	
High blood pressure headache	√		
Liver disorder nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine, abdominal pain			√
Pancreatic disorder acute or chronic abdominal pain (frequently radiating to the back), indigestion, nausea and vomiting, diarrhea, swollen and tender abdomen, bloating			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Coagulation disorder severe bruising or unusual bleeding from the skin or other areas			√
Uncommon			
Low level of red blood cells: tiredness, fatigue, pale skin			√
Reported from Post-Marketing with Unknown Frequency			
Increased ketones in urine or blood fruity scented breath, trouble breathing, confusion			√

This is not a complete list of side effects. For any unexpected effects while taking SIGNIFOR, contact your doctor or pharmacist.

HOW TO STORE IT

- Store between 15- 30°C.
- Keep this medicine out of the reach and sight of children.
- Store in the original package in order to protect from light.

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

If you want more information about SIGNIFOR:

- Talk to your healthcare professional
- This document plus the full product monograph, prepared for health professionals can be found at: www.recordatirarediseases.com/ca or by contacting the sponsor, Recordati Rare Diseases Canada Inc., at: 1-905-827-1300

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