

## Package leaflet: Information for the user

**Signifor 10 mg powder and solvent for suspension for injection**  
**Signifor 20 mg powder and solvent for suspension for injection**  
**Signifor 30 mg powder and solvent for suspension for injection**  
**Signifor 40 mg powder and solvent for suspension for injection**  
**Signifor 60 mg powder and solvent for suspension 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 acromegaly in adult patients. It is also used to treat Cushing's disease in adult patients for whom surgery is not an option or for whom surgery has failed.

#### Acromegaly

Acromegaly is caused by a type of tumour called a pituitary adenoma which develops in the pituitary gland at the base of the brain. The adenoma leads the body to over-produce hormones that control growth of tissues, organs and bones, resulting in an increase in the size of bones and tissues, especially in the hands and feet.

Signifor reduces the production of these hormones and possibly also the size of the adenoma. As a result, it reduces the symptoms of acromegaly, which include headache, increased sweating, numbness of the hands and feet, tiredness and joint pain.

#### Cushing's disease

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;
- or if you are taking anticoagulants (medicines used to reduce the clotting ability of the blood), your doctor will monitor your coagulation parameters and may adjust your anticoagulant dose.

During your treatment with Signifor:

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

### **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, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- If you are breast-feeding, ask your doctor for advice before taking this medicine, as 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 headache, dizziness 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**

This medicine will be given to you by a trained healthcare professional.

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

#### **Acromegaly**

The recommended starting dose of Signifor in acromegaly is 40 mg every 4 weeks. After you have started treatment, your doctor may reassess your dose. This may involve measuring the levels of growth hormone or other hormones in your blood. Depending on the results and how you are feeling, the dose of Signifor given in each injection may need to be reduced or increased. The dose should not exceed 60 mg. If you have liver disease before you start Signifor treatment for acromegaly, your doctor may want to start your treatment with a dose of 20 mg.

#### **Cushing’s disease**

The usual starting dose of Signifor in Cushing’s disease is 10 mg every 4 weeks. After you have started treatment, your doctor may reassess your dose. This may involve measuring the levels of cortisol in your blood or urine. Depending on the results and how you are feeling, the dose of Signifor given in each injection may need to be reduced or increased. The dose should not exceed 40 mg.

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 inject Signifor. If you have any questions, contact your doctor, nurse or pharmacist.

Signifor is intended for intramuscular use. This means that it is injected through a needle into the

muscles of your buttocks.

### **How long to use Signifor**

This is a long-term treatment, possibly lasting for years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect. Your treatment with Signifor should continue for as long as your doctor tells you that it is necessary.

### **If you stop using Signifor**

If you interrupt your treatment with Signifor 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)

- High 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.

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.
- Prolonged QT interval (an abnormal electrical signal in your heart that can be seen in tests).
- 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
- Abdominal pain
- Fatigue

Common (may affect up to 1 in 10 people)

- Tiredness, fatigue, pale skin (signs of low level of red blood cells)
- Loss of appetite
- Headache
- Bloating
- Vomiting
- Dizziness
- Pain, discomfort, pruritis and swelling at the injection site
- Change in liver function test results
- Abnormal blood test results (sign of high level of creatine phosphokinase, glycosylated haemoglobin, lipase in the blood)
- Hair loss

Uncommon (may affect up to 1 in 100 people)

- Change in pancreatic function blood test results (amylase)
- Abnormal blood coagulation properties

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.

### **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

### **United Kingdom**

Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

### **Ireland**

HPRA Pharmacovigilance

Website: [www.hpra.ie](http://www.hpra.ie)

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 carton, vial and pre-filled syringe after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze.
- 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 10 mg: each vial contains 10 mg pasireotide (as pasireotide pamoate).  
Signifor 20 mg: each vial contains 20 mg pasireotide (as pasireotide pamoate).  
Signifor 30 mg: each vial contains 30 mg pasireotide (as pasireotide pamoate).  
Signifor 40 mg: each vial contains 40 mg pasireotide (as pasireotide pamoate).  
Signifor 60 mg: each vial contains 60 mg pasireotide (as pasireotide pamoate).
- The other ingredients are:
  - In the powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).
  - In the solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

### **What Signifor looks like and contents of the pack**

Signifor powder is a slightly yellowish to yellowish powder in a vial. The solvent is a clear, colourless to slightly yellow or slightly brown solution in a pre-filled syringe.

Signifor 10 mg is available in unit packs containing one vial of powder with 10 mg pasireotide and one pre filled syringe with 2 ml solvent.

Signifor 20 mg is available in unit packs containing one vial of powder with 20 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Signifor 30 mg is available in unit packs containing one vial of powder with 30 mg pasireotide and one pre filled syringe with 2 ml solvent.

Signifor 40 mg is available in unit packs containing one vial of powder with 40 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Signifor 60 mg is available in unit packs containing one vial of powder with 60 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Each unit pack contains the vial and pre-filled syringe in a sealed blister tray with one vial adapter and one safety-engineered needle for injection.

Signifor 40 mg and Signifor 60 mg are also available in multipacks containing 3 intermediate packs.

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

### **Marketing Authorisation Holder**

Recordati Rare Diseases  
Immeuble Le Wilson  
70 avenue du Général de Gaulle  
92800 Puteaux  
France

### **Manufacturer**

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

Recordati Rare Diseases  
Immeuble Le Wilson  
70 avenue du Général de Gaulle  
92800 Puteaux  
France

Recordati Rare Diseases  
Eco River Parc  
30 rue des Peupliers  
92000 Nanterre  
France

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

### **United Kingdom & Ireland**

Recordati Rare Diseases UK Ltd.  
Tel: +44 (0)1491 414333

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### **Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website: <http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

**The following information is intended for healthcare professionals only:**

**INSTRUCTIONS FOR USE OF SIGNIFOR POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION**

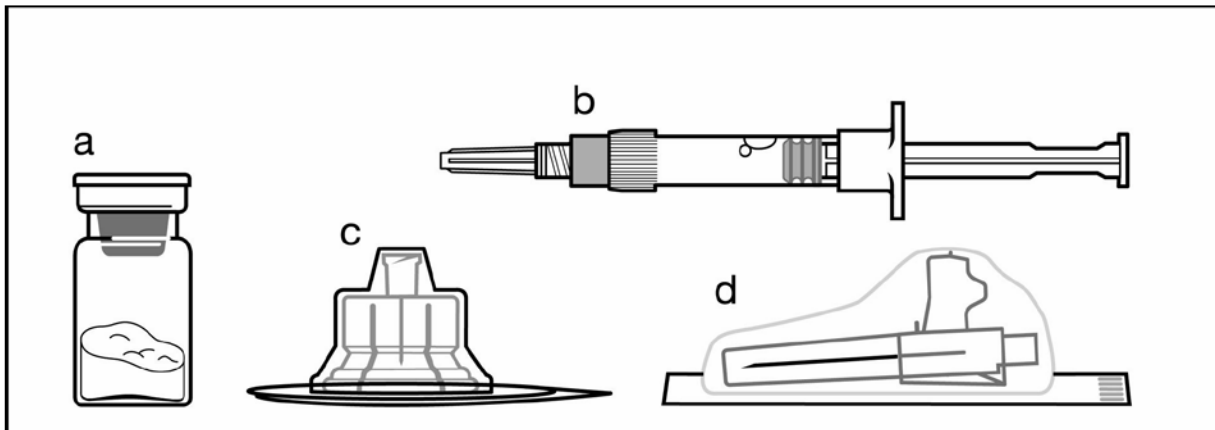
FOR DEEP INTRAMUSCULAR INJECTION ONLY.

**ATTENTION:**

There are two critical steps in the reconstitution of Signifor. **Not following them could result in failure to deliver the injection appropriately.**

- **The injection kit must reach room temperature.** Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the solvent, **shake the vial moderately** for a minimum of 30 seconds **until a uniform suspension is formed.**

**Included in the injection kit:**



- a One vial containing the powder
- b One pre-filled syringe containing the solvent
- c One vial adapter for medicinal product reconstitution
- d One safety injection needle (20G x 1.5")

Follow the instructions below carefully to ensure proper reconstitution of Signifor powder and solvent for suspension for injection before deep intramuscular injection.

Signifor suspension must only be prepared immediately before administration.

Signifor should only be administered by a trained healthcare professional.

**Step 1**

Remove the Signifor injection kit from refrigerated storage.

**ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.**

Note: If not used within 24 hours, the injection kit can be returned to the fridge.



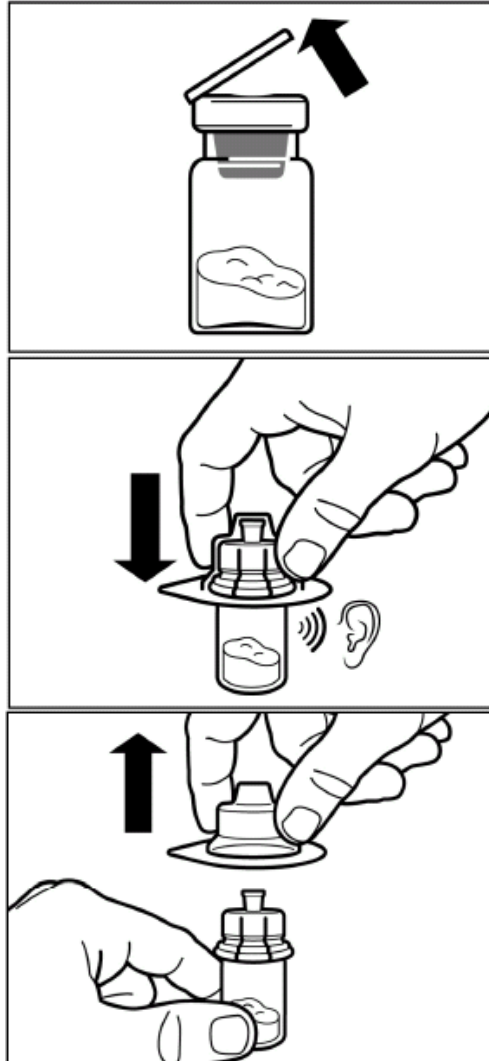
**Step 2**

Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.

Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.

Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by a “click”.

Remove the packaging from the vial adapter by lifting it straight up as shown.

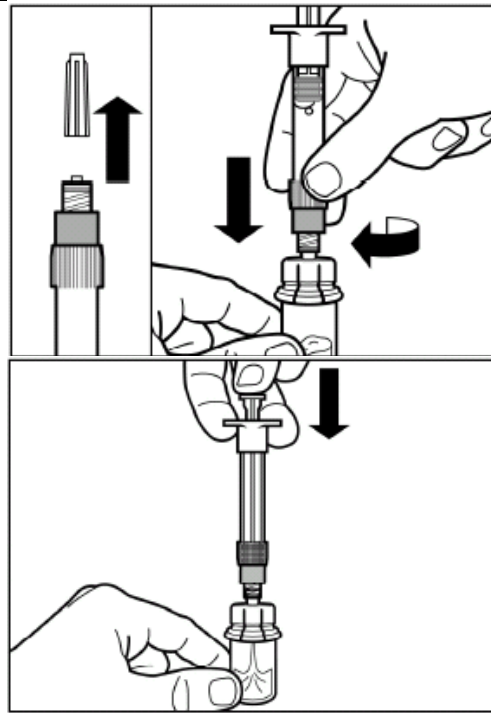




**Step 3**

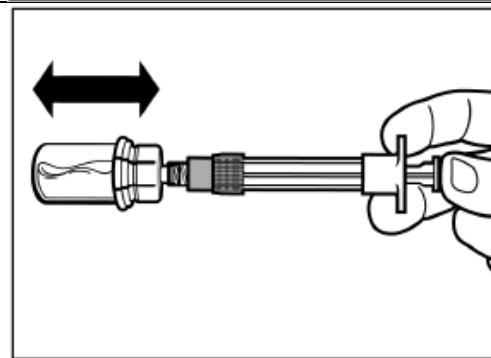
Remove the cap from the syringe pre-filled with solvent and **screw** the syringe onto the vial adapter.

Slowly push the plunger all the way down to transfer all the solvent in the vial.



**Step 4**

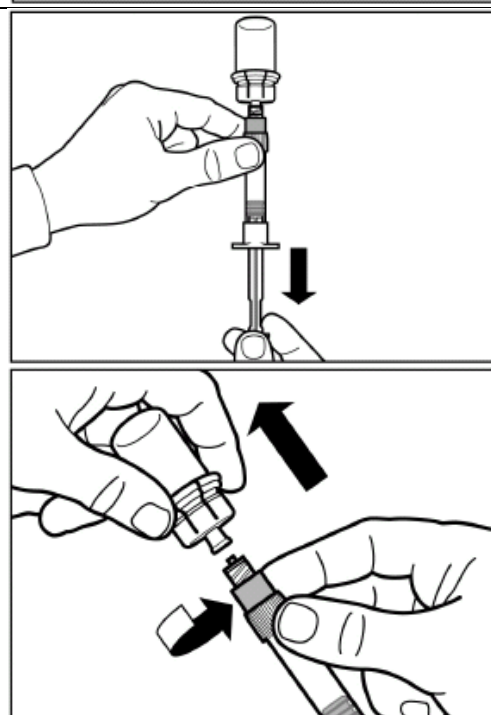
**ATTENTION:** Keep the plunger pressed and shake the vial **moderately for a minimum of 30 seconds** so that the powder is completely suspended. **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**



**Step 5**

Turn syringe and vial upside down, **slowly** pull the plunger back and draw the entire content from the vial into the syringe.

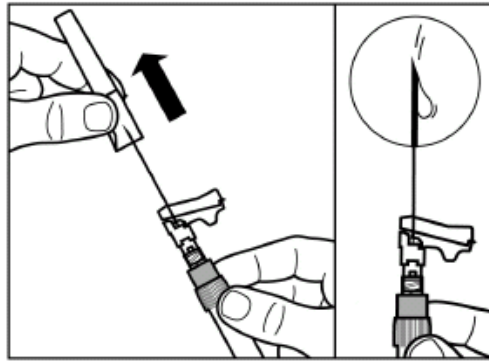
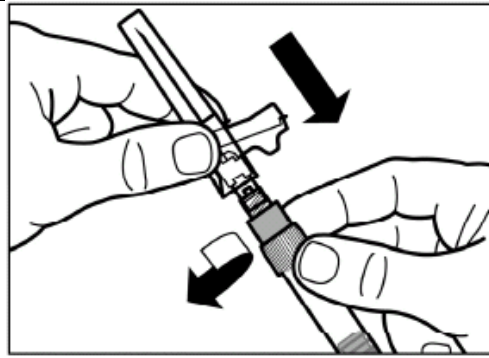
Unscrew the syringe from the vial adapter.



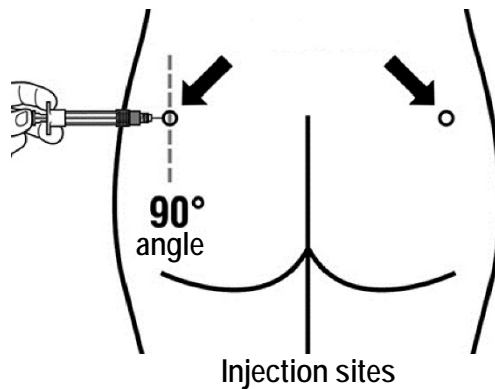
**Step 6**

Screw the safety injection needle onto the syringe.

Pull the protective cover straight off the needle. To avoid sedimentation, you may gently shake the syringe to maintain a uniform suspension. Gently tap the syringe to remove any visible bubbles and expel them from the syringe. The reconstituted Signifor is now ready for **immediate** administration.

**Step 7**

Signifor must be given only by deep intramuscular injection. Prepare the injection site with an alcohol wipe. Insert the needle fully into the left or right gluteus at a 90° angle to the skin. Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated). Slowly depress the plunger until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in Step 8).

**Step 8**

Activate the safety guard over the needle, in one of the two methods shown:

- either press the hinged section of the safety guard down onto a hard surface (figure A),
- or push the hinge forward with your finger (figure B).

An audible “click” confirms proper activation.

Dispose of syringe immediately in a sharps container.

