NOVARTIS

Signifor®

Composition

Active substance: Pasireotide (as pasireotide diaspartate)

Excipients: Mannitol, tartaric acid, sodium hydroxide, water for injections.

Pharmaceutical form and quantity of active substance per unit

Solution for injection in ampoules.
Clear, colourless solution.
Each 1 ml ampoule contains 0.3 mg pasireotide.
Each 1 ml ampoule contains 0.6 mg pasireotide.
Each 1 ml ampoule contains 0.9 mg pasireotide.

Indications/Potential uses

Treatment of patients with Cushing's disease when all non-drug treatment alternatives according to current standards have been exhausted.

Dosage/Administration

Adults

The recommended initial dose of Signifor is subcutaneous (s.c.) injection of 0.6 mg twice daily.

In the event of suspected adverse effects, the Signifor dose may be temporarily reduced. Dose reduction in 0.3 mg steps twice daily is recommended.

One month after starting treatment with Signifor, patients should be evaluated for clinical benefit. A dose increase to 0.9 mg (twice daily) may be considered in those responding to treatment, as long as the 0.6 mg dose is well tolerated by the patient. Patients who have not responded to Signifor after two months of treatment should be considered for discontinuation. Patients with a clinically significant reduction in urinary free cortisol [UFC] and improvement in signs and symptoms of the disease should continue treatment with Signifor for as long as they benefit from it. Maximum UFC reduction is typically seen after two months of treatment.

Special patient populations

Patients with renal impairment

Dose adjustment is not required in patients with impaired renal function.

Patients with hepatic impairment

Dose adjustment is not required in patients with mild hepatic impairment (Child-Pugh A). The recommended initial dose for patients with moderate hepatic impairment (Child-Pugh B) is 0.3 mg twice daily. The maximum recommended dose for patients with moderate hepatic impairment is 0.6 mg twice daily. Signifor should not be used in patients with severe hepatic impairment (Child-Pugh C) (see "Contraindications").

Children and adolescents

The efficacy and safety of use in children and adolescents have not been studied.

Elderly patients

Data on the use of Signifor in patients over 65 years of age are limited. There is no evidence that dose adjustment is required in elderly patients.

Contraindications

Hypersensitivity to the active substance or any of the excipients.
Severe hepatic impairment (Child-Pugh C).

Warnings and precautions

Hypocortisolism

Treatment with Signifor leads to rapid suppression of adrenocorticotropic hormone (ACTH) secretion. Rapid suppression of ACTH may lead to transient hypercortisolism with the signs weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia or hypoglycaemia and even Addisonian crisis. Cases of hypocortisolism have been reported in the phase III study, generally within the first two months of treatment. Depending on the clinical situation, it may be necessary to discontinue treatment, reduce the dose of Signifor and/or give low-dose, short-term glucocorticoid therapy.

Patients should be regularly monitored and informed about the symptoms associated with hypocortisolism.

Glucose metabolism

Changes in glucose regulation are likely during treatment of Cushing's disease with pasireotide. Hyperglycaemia, raised fasting blood glucose, an increase in HbA1c and, less often, hypoglycaemia have been observed in clinical studies of pasireotide. The development of hyperglycaemia correlates with decreased secretion of insulin and incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). The degree of glucose deregulation is higher in patients with prediabetic metabolic status or frank diabetes.

Glycaemic status (fasting blood glucose and HbA1c) should be assessed before starting treatment and regularly monitored during treatment. Self-monitoring of blood glucose and FPG/HbA1c levels should be done every week for the first two to three months of treatment and periodically thereafter at clinically appropriate intervals. FPG levels should be monitored for three weeks, and HbA1c levels for three months after the end of treatment.

If hyperglycaemia occurs, initiation or adjustment of hyperglycaemia therapy with incretins, insulin secretagogues and/or insulin is indicated. If hyperglycaemia cannot be controlled despite appropriate medical measures, the Signifor dose should be reduced or treatment discontinued. Cushing's disease patients with poor glycaemic control (defined as HbA1c values >8% on antidiabetic therapy) are at higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). In patients with poor glycaemic control, diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy.

Cardiovascular events

Bradycardia has been observed during treatment with pasireotide. Patients with cardiac disease and/or risk factors for bradycardia – such as a history of clinically significant bradycardia, acute myocardial infarction or Mobitz type II block, congestive heart failure (NYHA class III or IV), unstable angina, ventricular tachycardia or ventricular fibrillation – must be carefully monitored. It may be necessary to adjust the dose of drugs such as beta blockers, calcium channel blockers or agents to control electrolyte balance.

Pasireotide was shown to prolong the QT interval in the ECG in a study in healthy volunteers. The clinical significance of this prolongation is unknown. A QTcF value of >500 ms was measured in two of 201 patients. These episodes were sporadic and occurred once only with no clinical consequence. Episodes of torsade de pointes were not observed, either in these studies or in clinical studies in other patient populations.

Pasireotide should be used with caution in patients at significant risk of QT interval prolongation, such as those:

- with congenital long QT syndrome,
- with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia,
- taking antiarrhythmics or other substances with known potential for QT prolongation,
- with hypokalaemia and/or hypomagnesaemia.

Monitoring for a possible effect on the QTc interval is advisable and a baseline ECG is recommended before starting treatment with Signifor and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected before treatment with Signifor and should be monitored periodically during treatment.

Liver function tests

Transient mild elevations in aminotransferases are commonly observed in healthy subjects and patients treated with pasireotide. Concurrent elevation of alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) and bilirubin >2 × ULN has been observed in rare cases. All cases of concurrent elevation were identified within 10 days of starting treatment with Signifor, all individuals recovered without clinical sequelae and liver function test results returned to baseline after interruption of treatment. Monitoring of liver function is therefore recommended before and during the first two to three months of treatment with Signifor (after 1, 2, 4, 8 and 12 weeks), and thereafter if clinically indicated.

Patients with elevated transaminase levels should have a second liver function test to confirm the results. If levels are elevated, liver function tests should be performed frequently until the patient returns to pre-treatment levels.

Treatment with pasireotide should be discontinued if patients develop jaundice or other signs of clinically significant hepatic impairment, or in the event of an increase in aspartate aminotransferase (AST) or ALT >5 × ULN or an increase in ALT >3 × ULN with concurrent bilirubin elevation >2 × ULN. Following discontinuation of treatment, patients should be monitored until recovery. Treatment should not be restarted.

Gallbladder

Gallstone formation is a known adverse effect of long-term treatment with somatostatin analogues and has been frequently observed in clinical studies of pasireotide. Ultrasound examination of the gallbladder is therefore recommended before treatment with Signifor and then at 6- to 12-month intervals. The occurrence of gallstones in Signifor-treated patients is largely asymptomatic; symptomatic stones should be managed according to clinical practice.

Pituitary hormones

Deficiency of pituitary-secreted hormones is a common sequela of transsphenoidal surgery and even more common after pituitary radiotherapy. Cushing's disease patients with persistent or recurrent disease may therefore present with deficiency of one or more pituitary hormones. As the pharmacological effect of pasireotide mimics that of somatostatin, inhibition of other pituitary hormones in addition to ACTH cannot be ruled out. Pituitary function (e.g. TSH/free T_4, GH/IGF-1) should therefore be monitored before starting treatment with Signifor and periodically during treatment, as clinically appropriate.

Fertility

The effect of pasireotide on human fertility is unknown; it should be borne in mind when treating women of childbearing potential that female fertility might be reduced.

Interactions

No clinical studies have been performed to assess drug-drug interaction potential.

Caution is required when coadministering Signifor with antiarrhythmic agents or drugs that may prolong the QT interval (see "Warnings and precautions").

Anticipated interactions affecting other drugs

Pasireotide has moderate protein binding, is metabolically stable and is not a substrate, inhibitor or inducer of CYP450 *in vitro*. Pasireotide appears to be a substrate of efflux transporter Pgp (P-glycoprotein). However, pasireotide is not an inducer of Pgp at clinically relevant concentrations. Pasireotide is not a substrate of the efflux transporter breast cancer resistance protein (BCRP), nor of the influx transporters organic cation transporter 1 (OCT1), organic anion-transporting polypeptides (OATP) 1B1, 1B3 or 2B1. At clinically relevant concentrations, pasireotide is not expected to inhibit UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1), influx transporters OATP 1B1 or 1B3, efflux transporters Pgp, BCRP, MRP2 (multiresistance protein 2) or BSEP (bile salt export pump).

Limited published data suggest that somatostatin analogues might indirectly reduce metabolic clearance of compounds metabolized by CYP450 enzymes by suppressing growth hormone secretion. Available data cannot exclude the possibility that pasireotide may exert such an indirect effect. Caution is required when administering pasireotide concomitantly with drugs that have a low therapeutic index and are metabolized mainly by CYP3A4 (e.g. quinidine, terfenadine).

In dogs, pasireotide has been found to decrease the blood level of ciclosporin by reducing its intestinal absorption. It is unknown whether such interaction occurs in humans. Ciclosporin dose adjustment may therefore be necessary when coadministering pasireotide and ciclosporin.

Coadministration of bromocriptine with somatostatin analogues may increase the availability of bromocriptine. The possibility cannot be excluded that pasireotide may exert such an effect.

Pregnancy/Breastfeeding

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in rats and rabbits have shown evidence of fetal damage by pasireotide at therapeutic exposure levels (see "Preclinical data"). Reproductive toxicity studies in animals are not always indicative of the response in humans. Signifor should only be used during pregnancy under compelling circumstances.

Breastfeeding

It is not known whether pasireotide is excreted in human milk. Studies in rats have shown excretion of pasireotide in milk (see "Preclinical data"). As a risk to the breastfed child cannot be excluded, patients should not breastfeed during treatment with Signifor.

Effects on ability to drive and use machines

Pasireotide has no effect on the ability to drive or use machines.

Adverse effects

A total of 201 Cushing's disease patients received treatment with Signifor in the phase II and III studies. The tolerability profile is consistent with that of the somatostatin analogue class, except for the occurrence of hypocortisolism and degree of hyperglycaemia.

The data described below relate to 162 Cushing's disease patients treated with Signifor 0.6 mg or 0.9 mg twice daily in the phase III study. The frequency and severity of adverse effects were similar in the two dose groups. Most effects were grade 1 or 2 (57.4%). Grade 3 and 4 adverse effects were observed in 35.8% and 2.5% of patients, respectively, and were mostly related to hyperglycaemia. The most common ADRs (incidence >10%) were diarrhoea, nausea, abdominal pain, cholelithiasis, hyperglycaemia, diabetes mellitus, fatigue and increased HbA1c.

The following adverse effects were reported in clinical studies of pasireotide, and are listed below according to MedDRA terminology.

Frequencies were defined as follows: *very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100).*

Adverse effects are ranked in order of decreasing seriousness within each frequency grouping.

Endocrine disorders

Common: Adrenocortical insufficiency.

Metabolism and nutrition disorders

Very common: Hyperglycaemia, diabetes mellitus.

Common: Type 2 diabetes mellitus, decreased appetite.

Nervous system disorders

Common: Headache.

Cardiac disorders

Common: Sinus bradycardia, QT prolongation.

Gastrointestinal disorders

Very common: Diarrhoea, nausea, abdominal pain.

Common: Vomiting, upper abdominal pain.

Hepatobiliary disorders

Very common: Cholelithiasis.

Skin and subcutaneous tissue disorders

Common: Alopecia.

Vascular disorders

Common: Hypotension.

Blood and lymphatic disorders

Uncommon: Anaemia.

General disorders and administration site conditions

Very common: Injection site reactions, fatigue.

Investigations

Very common: Glycosylated haemoglobin increased.

Common: Gamma-glutamyltransferase increased, alanine aminotransferase increased, lipase increased, blood glucose increased, blood amylase increased, prothrombin time prolonged.

Overdose

No cases of overdosage have been reported in patients receiving pasireotide subcutaneously. Doses up

to 2.1 mg twice daily have been administered to healthy volunteers, leading to diarrhoea as a very frequent adverse effect.

In the event of overdosage, it is recommended that appropriate supportive treatment be initiated, as dictated by the patient's clinical status, until resolution of the symptoms.

Properties/Actions

ATC code: H01CB05

Mechanism of action

Pasireotide (cyclohexapeptide) is a somatostatin analogue that binds with high affinity to human somatostatin receptor subtypes hsst 1, 2, 3 and 5.

Pharmacodynamic properties

Somatostatin receptors are expressed in many tissues, as well as in neuroendocrine tumours.

In vitro studies have shown that corticotroph tumour cells from Cushing's disease patients display high expression of hsst5, whereas other receptor subtypes are either not expressed or are expressed at lower levels. Pasireotide binds and activates the hsst receptors of the corticotrophs in ACTH-producing adenomas, resulting in inhibition of ACTH secretion.

Glucose metabolism

In a phase I study in healthy volunteers, pasireotide was administered with or without oral antidiabetics (metformin, nateglinide, vildagliptin, liraglutide) for 7 days. An oral glucose tolerance test was performed before the start of treatment and on day 7. After the first pasireotide dose, glucose AUC increased by more than 100% relative to baseline in all 5 study arms. On day 7 the difference from baseline was 69% without antidiabetics, compared to 60% on comedication with metformin, 49% on nateglinide, 38% on vildagliptin and 19% on liraglutide. This correlated with a 79% decrease in insulin secretion, which was partially antagonized by vildagliptin and liraglutide. Metformin had no material effect.

Cardiac electrophysiology

The effect of Signifor on the QT interval was assessed in two open-label, controlled, cross-over dedicated QT studies. In both studies an effect of pasireotide on the QT interval was observed. One of the studies, with a dose of 1950 µg twice daily, measured a maximum mean placebo-adjusted QTcF value of 17.5 ms (90% confidence interval [CI]: 15.53; 19.38). The other study found maximum mean placebo-adjusted QTcI values of 13.19 ms (90% CI: 11.38; 15.01) and 16.12 ms (90% CI: 14.30; 17.95 ms), respectively, at the doses of 600 µg and 1950 µg twice daily. At both doses there was a reduction in heart rate, with a maximum difference from placebo observed after 1 hour for pasireotide 600 µg twice daily (-10.39 bpm) and after 30 minutes for pasireotide 1950 µg twice daily (-14.91 bpm).

Clinical efficacy

In a double-blind, multicentre, randomized phase III study, 162 patients with persistent or recurrent Cushing's disease following adenoma resection and patients for whom surgery was not indicated or who refused surgery were treated for 12 months with either 0.6 mg or 0.9 mg pasireotide twice daily.

After three months of treatment, patients who had a mean 24-hour UFC ≤2 × ULN and values at or below baseline continued blinded treatment at the randomized dose until month 6. Patients who did not meet these criteria were unblinded and the dose was increased by 0.3 mg twice daily. After 6 months of treatment, patients started an additional 6-month open-label treatment period. If response was not achieved after 6 months or not maintained during the open-label treatment period, the subcutaneous dose could be increased by 0.3 mg twice daily. The maximum injected dose was 1.2 mg s.c. twice daily. The dose could be reduced in steps of 0.3 mg twice daily at any time for intolerability.

The primary efficacy endpoint was the proportion of patients in each arm who achieved normalization of mean 24-hour urinary free cortisol levels (UFC ≤ULN) after 6 months of treatment and who did not have a dose increase (relative to randomized initial dose) during this period. Secondary endpoints included changes from baseline in 24-hour UFC, plasma ACTH, serum cortisol levels, clinical signs and symptoms of Cushing's disease and health-related quality of life (HRQL) as measured by the CushingQoL. All analyses were based on the randomized dose groups.

Baseline characteristics were balanced between the two dose groups, except for a large difference in mean 24-hour UFC (1156 nmol/24 h for the 0.6 mg twice daily group and 781 nmol/24 h for the 0.9 mg twice daily group; normal range 30-145 nmol/24 h).

After 6 months, normalization of mean UFC levels was observed in 14.6% (95% CI 7.0 to 22.3) and 26.3% (95% CI 16.6 to 35.9) of patients, respectively, in the pasireotide 0.6 mg and 0.9 mg twice daily treatment groups.

The study met the primary efficacy objective in the 0.9 mg twice daily dose group, as the lower limit of the 95% CI is greater than the predefined 15% boundary. However, this response in the 0.9 mg twice daily group seemed to be higher for patients with lower mean UFC at baseline. In both dose groups Signifor led to a rapid and marked decrease in mean UFC after 1 month, which was maintained throughout the treatment period. The response rate after 12 months was comparable to that after 6 months, amounting to 13.4% and 25.0% in the 0.6 mg and 0.9 mg twice daily dose groups, respectively. The controlled and partially controlled response rates after 6 months represented 34% (0.6 mg twice daily) and 41% (0.9 mg twice daily) of randomized patients (controlled: UFC ≤1.0 × ULN, partially controlled: UFC >1.0 × ULN, but ≥50% decrease in UFC). Patients uncontrolled at both months 1 and 2 were likely (90%) to remain uncontrolled at months 6 and 12.

A significant reduction in median UFC levels was noted in both treatment arms. After 6 months the median percentage reduction in UFC levels was 47.9% in both treatment groups (0.6 mg and 0.9 mg twice daily); after 12 months the percentage UFC reduction was 67.6% and 62.4% for the 0.6 mg and 0.9 mg twice daily groups, respectively. Clinically meaningful decreases in sitting systolic and diastolic blood pressure, BMI and total cholesterol were observed in both dose groups after 6 months. Similar trends were observed after 12 months, with the addition of serum triglycerides also decreasing at that time point.

After 6 months a third of patients in both dose groups showed favourable changes in facial rubor, supraclavicular and dorsal fat pads and median global CushingQoL scores.

Pharmacokinetics

Absorption

Pasireotide is rapidly and completely absorbed after SC injection, and peak plasma concentrations are reached within 0.25-0.5 hours. C_{max} and AUC are approximately dose-proportional after both single and multiple dosing.

Distribution

Pasireotide has a volume of distribution (V_z/F) of >100 litres. Pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

Pasireotide is likely to be a substrate of Pgp; it has not been studied for ability to penetrate the cerebrospinal fluid.

Metabolism

Pasireotide was shown to be highly metabolically stable in human liver and kidney microsomes.

Pasireotide displays low clearance in healthy volunteers (6.7 litres/hour) and Cushing's disease patients (3.8 litres/hour). It has a long effective half-life ($t_{1/2}$ approximately 12 hours) in healthy volunteers.

Elimination

Pasireotide is eliminated intact mainly via hepatic clearance (biliary excretion) and only to a small extent by the kidney. 55.9 ± 6.63% of radiolabelled pasireotide was recovered over the first 10 days post dosing, including 48.3 ± 8.16% of the radioactivity in faeces and 7.63 ± 2.03% in urine.

Special patient populations

Elderly patients

Data on Cushing's disease patients older than 65 years are limited but do not suggest any clinically significant differences in safety and efficacy compared to younger patients.

Children

No studies have been performed in children.

Patients with renal impairment

Clinical studies have not been performed in patients with impaired renal function.

Patients with hepatic impairment

In a clinical study in subjects with impaired hepatic function (Child-Pugh A, B and C), only subjects with moderate to severe hepatic impairment (Child-Pugh B and C) showed significantly elevated exposures compared to patients with normal hepatic function. After correction for covariate effect (age, BMI and albumin), AUC_{inf} was increased by 60% to 79%, C_{max} increased by 67% to 69%, and CL/F decreased by 37% and 44% compared to the control group.

Demographics

Population PK analyses of Signifor suggest that race and gender do not influence PK parameters.

Preclinical data

Non-clinical safety studies included safety pharmacology, repeated-dose toxicity, genotoxicity and carcinogenicity, and reproductive and developmental toxicity. Most findings in the repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. The main findings were lower pituitary weight and somatotroph eosinophilia (rat) or increased pituitary acidophilia (monkey), inhibition of body weight gain and growth (including bone growth in rodents), reduced liver weight and increased liver enzyme levels (rodents), and reduced cellularity of haematopoietic organs. The effects in non-clinical studies were generally observed at exposures similar to or greater than the maximum exposure to human therapeutic doses.

In safety pharmacology studies, pasireotide had no adverse effects on respiratory or cardiovascular functions. Decreases in general and behavioural activity were observed in mice at a dose of 12 mg/kg, equivalent to 32 times the maximum recommended human dose (MRHD), based on surface area.

Pasireotide was found non-genotoxic in two *in vitro* genotoxicity tests (Ames test and chromosome aberration test in human peripheral lymphocytes). Pasireotide was not genotoxic in an *in vivo* rat micronucleus test at doses up to 50 mg/kg, approximately 250 times the maximum recommended therapeutic human dose (MRHD), based on surface area.

Carcinogenicity studies conducted in rats and transgenic mice did not identify any carcinogenic potential.

In embryo-fetal development studies in rats and rabbits, pasireotide was not teratogenic at maternally toxic doses (corresponding to 10 [rat] and 1 [rabbit] mg/kg/day) leading to exposures (AUC_{0-24h}) 145 [rat] and 6.5 [rabbit] times exposure at the MRHD. At 10 mg/kg/day in rats, the frequency of early/total resorptions and malrotated limbs was increased. At 5 mg/kg/day in rabbits (corresponding to 40 times exposure at MRHD), increased abortions, reduced fetal weights and ensuing skeletal variations were observed. Reduced fetal weight and ensuing delayed ossification were seen at 1 mg/kg/day (6.5 times exposure at MRHD). In a pre- and postnatal study in rats, pasireotide had no effect on labour or delivery at doses up to 10 mg/kg/day (52 times MRHD, based on surface area). Pasireotide is excreted in milk. Retardation of physiological growth in the offspring was seen at 2 mg/kg/day (10 times MRHD, based on surface area). After weaning, body weight gains in the rat pups exposed to pasireotide were comparable to controls, indicating reversibility. Pasireotide did not affect fertility in male rats at doses up to 10 mg/kg/day (52 times MRHD, based on surface area). Animal studies showed that fertility in female rats decreased at daily doses of 0.1 mg/kg/day (0.6 times MRHD, based on surface area), as shown by decreased numbers of live conceptions and implantation sites. A reduced number of corpora lutea and abnormal cycles or acyclicity were observed at 1 mg/kg/day (5 times MRHD, based on surface area).

Other information

Incompatibilities

No compatibility data with other products have been generated. Pasireotide solution for injection is to be used undiluted and must not be mixed with other medicinal products.

Administration

Signifor is administered subcutaneously by self-injection. Patients must be instructed by the physician or healthcare professional how to inject Signifor subcutaneously.

Repeated injections within a short period at the same or a nearby injection site should be avoided. Sites showing signs of irritation or inflammation should be avoided. Preferred injection sites are the thighs and abdomen (excluding the navel and waistline).

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Keep out of the reach of children.

Store in the original pack and protect from light. Do not store above 30°C.

Instructions for use and handling

The solution for injection is supplied in a 1 ml glass ampoule.

To ensure proper administration of the product, the patient should be instructed by a physician or other healthcare professional how to use Signifor from the ampoule. Refer to the package leaflet (patient information) for further instructions on the use of Signifor from the ampoule.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Pack sizes

Ampoules containing 0.3 mg: packs of 30 ampoules (5 boxes containing 6 ampoules)

Ampoules containing 0.6 mg: packs of 30 ampoules (5 boxes containing 6 ampoules)

Ampoules containing 0.9 mg: packs of 30 ampoules (5 boxes containing 6 ampoules)

Other country specific pack sizes, as applicable.

Instructions for use of Signifor

Signifor should be administered using sterile disposable syringes and injection needles.

Your doctor or nurse will have instructed you on how to use Signifor ampules. However, before using the ampule, 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 or nurse for help.

Store Signifor ampules according to the storage condition listed on the box.

Important safety information

Caution: Keep the ampules out of the reach of children. What do you need to give yourself a subcutaneous injection

1. One Signifor ampule
2. Alcohol wipes or similar
3. One sterile syringe
4. One sterile needle
5. 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

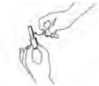
- When you are ready to give yourself the injection, carefully follow the steps below:Wash your hands thoroughly with soap and water. Always use a new disposable needle and syringe every time you give yourself an injection.
- Use syringes and needles only once. **Never** share needles and syringes with someone else.
- Take the ampule out of the box.Carefully inspect the ampule. 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.

Check the expiry date and the dose:

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

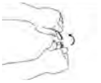
DO NOT USE if the medicine has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

How to inject Signifor

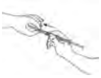


Before you proceed to Step 1, clean the injection site you have selected with an alcohol swab.

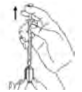
Step 1: Signifor solution for injection is filled in a snap-off ampule. Tap the ampule with your finger in order to make sure there is no liquid in the lid when you open the ampule.



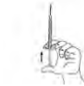
Step 2: Open it by snapping off the top of the ampule at the line marked on the ampule neck. Once open, put the ampule upright on a clean, flat surface.



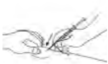
Step 3: Take the sterile syringe and attach the needle to it. Remove the cover from the needle.



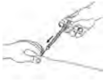
Step 4: Put the needle into the ampule and pull the plunger to draw the entire contents of the ampule into the syringe.



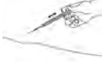
Step 5: Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger. Tap the syringe with your fingers to get rid of air bubbles. Make sure there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.
Do not let the needle touch anything. You are now ready to inject.



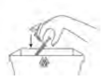
Step 6: Gently pinch the skin at the injection site and, holding the needle at an angle of approximately 45 degrees (as shown in the picture) insert it into the injection site.
Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle 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 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.

Manufacturer

Novartis Pharma Stein AG, Stein, Switzerland

Marketing authorization holder

Novartis Pharma Schweiz AG, Risch, Switzerland

Information last revised

August 2013

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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