NOVARTIS

Signifor®

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Solution for injection

Active substance

Each ampule of 1 mL contains:

Signifor® 0.3mg - 0.3 mg pasireotide (as diaspartate).

Signifor® 0.6mg - 0.6 mg pasireotide (as diaspartate).

Signifor® 0.9mg - 0.9 mg pasireotide (as diaspartate).

Certain dosage strengths may not be available in all countries.

Active moiety

Pasireotide

Excipients

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

Information might differ in some countries.

INDICATIONS

Treatment of patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

DOSAGE AND ADMINISTRATION

Dosage

General target population

Adult patients

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

Two months after the start of Signifor therapy, patients should be evaluated for clinical benefit. Patients who experience a significant reduction in urinary free cortisol [UFC] levels should continue to receive Signifor for as long as benefit is derived. A dose increase to 0.9 mg

may be considered based on the response to the 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.

Management of suspected adverse reactions at any time during the treatment may require temporary dose reduction of Signifor. Dose reduction by decrements of 0.3 mg twice a day is suggested.

If a dose of Signifor is missed, the next injection should be administered at the scheduled time. Doses should not be doubled to make up for a missed dose.

Special populations

Patients with renal impairment

No dose adjustment is required in patients with impaired renal function (see section CLINICAL PHARMACOLOGY).

Patients with hepatic impairment

Dose adjustment is not required in patients with mildly impaired hepatic function (Child-Pugh A). For patients with moderately impaired hepatic function (Child-Pugh B) the recommended initial dose is 0.3 mg twice a day (see section CLINICAL PHARMACOLOGY). The maximum recommended dose is 0.6 mg twice a day. Signifor should not be used in patients with severe hepatic impairment (Child Pugh C) (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Pediatric patients

Signifor is not recommended for use in pediatric Cushing's disease patients as there are no clinical data available in patients under 18 years of age.

Geriatric patients (65 years of age or older)

There are limited data on the use of Signifor in patients older than 65 years but there is no evidence suggesting that a dose adjustment is required in elderly patients (see section CLINICAL PHARMACOLOGY).

Method of administration

Signifor is to be administered subcutaneously by self-injection. Patients should receive instructions from the physician or a health care professional on how to inject Signifor subcutaneously.

Use of the same injection site for two consecutive injections is not recommended. Sites showing signs of inflammation or irritation should be avoided. Preferred injection sites for subcutaneous injections are the top of the thighs and the abdomen (excluding the navel and waistline).

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh C).

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hypocortisolism

Treatment with Signifor leads to a rapid suppression of ACTH (adrenocorticotropic hormone) secretion in Cushing's disease patients. As with any other successful pituitary directed therapy, rapid and complete or near complete suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially to transient hypocortisolism/hypoadrenalism.

Cases of hypocortisolism have been reported in the Phase III study in Cushing's disease patients (see section ADVERSE DRUG REACTIONS), generally within the first two months of treatment. Except for one case in which treatment was discontinued, all other cases were manageable by reducing the dose of Signifor and/or adding low-dose, short-term glucocorticoid therapy.

It is therefore necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatremia or hypoglycemia). In case of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of treatment with Signifor may be necessary.

Glucose metabolism

Alterations in blood glucose levels have been seen in healthy volunteers and patients treated with pasireotide. Hyperglycemia, and less frequently hypoglycemia were observed in subjects participating in clinical trials with pasireotide (see section ADVERSE DRUG REACTION).

The development of hyperglycemia appears to be related to decrease in secretion of insulin (particularly in the post-dose period) as well as incretin hormones (i.e. Glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). The degree of hyperglycemia appeared to be higher in patients with pre-diabetic conditions or established diabetes mellitus. Treatment initiation with anti-diabetic agents was associated with decreases in HbA1C <7% and FPG <130 mg/dL in 43% and 72% of Cushings disease patients, respectively. During the pivotal study, HbA1c levels increased significantly and stabilised but did not return to baseline values. More cases of discontinuation and a higher reporting rate of severe adverse events due to hyperglycemia were reported in patients treated with the dose of 0.9 mg twice daily.

Glycemic status (fasting plasma glucose/hemoglobin A1c [FPG/HbA1c]) should be assessed prior to starting treatment with pasireotide. FPG/HbA1c monitoring during treatment should follow established guidelines. Self-monitoring of blood glucose and/or FPG assessments should be done weekly for the first two to three months and periodically thereafter, as clinically appropriate, as well as over the first two to four weeks after any dose increase. After treatment discontinuation, glycemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

If hyperglycemia develops in a patient treated with Signifor the initiation or adjustment of anti-diabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycemia. If uncontrolled hyperglycemia persists despite appropriate medical management the dose of Signifor should be reduced or the treatment discontinued.

Cushing's disease patients with poor glycemic control (as defined by HbA1c values >8% while receiving anti-diabetic therapy) may be at a higher risk of developing severe

hyperglycemia and associated complications (e.g. ketoacidosis). In patients with poor glycemic control, diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy.

Cardiovascular related events

Bradycardia has been reported with the use of pasireotide (see section ADVERSE DRUG REACTIONS). Patients with cardiac disease and/or risk factors for bradycardia, such as: history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, should be carefully monitored. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control electrolyte balance, may be necessary.

Pasireotide administered as Signifor s.c. has been shown to prolong the QT interval n healthy subjects based on two studies (see section CLINICAL PHARMACOLOGY). Additional analysis of thorough QT study data, including quantitative ECG beat to beat restitution analysis, showed that pasireotide does not alter cardiac repolarization in the same manner as drugs known to prolong QT that are associated with pro-arrhythmia (see section CLINICAL PHARMACOLOGY / Cardiac electrophysiology).

In clinical studies in Cushing's disease patients, QTcF of >500 msec was observed in two out of 201 patients. These episodes were sporadic and of single occurrence with no clinical consequence observed. Episodes of torsades de pointes were not observed in any clinical study with pasireotide.

Pasireotide should be used with caution in patients who are at significant risk of developing prolongation of QT, 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 anti-arrhythmic medicinal products or other substances that are known to lead to QT prolongation (see section INTERACTIONS),
- with hypokalemia and/or hypomagnesemia.

A baseline ECG is recommended prior to initiating therapy with Signifor. Monitoring for an effect on the QTc interval is advisable when starting treatment with Signifor and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to Signifor administration and electrolytes should be monitored periodically during therapy.

Liver tests

Mild transient elevations in aminotransferases are commonly observed in healthy subjects and patients treated with pasireotide. A few cases of concurrent elevations in ALT (alanine aminotransferase) greater than 3 x ULN (upper limit normal) and bilirubin greater than 2 x ULN have also been observed (see section ADVERSE DRUG REACTIONS). Monitoring of liver function is recommended prior to treatment with Signifor and after the first 1 to 2 weeks and then monthly for 3 months on treatment. Thereafter liver function should be monitored as clinically indicated.

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be

followed with frequent liver function monitoring until values return to pre-treatment levels. Therapy with pasireotide should be discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver impairment, in the event of a sustained increase in AST (aspartate aminotransferase) or ALT of 5 x ULN or greater, or if ALT or AST elevations greater than 3 x ULN occur concurrently with bilirubin elevations greater than 2 x ULN. Following discontinuation of treatment with pasireotide, patients should be monitored until resolution. Treatment should not be restarted if the liver function abnormalities are suspected to be related to Signifor.

Gallbladder and related events

Cholelithiasis is a recognized adverse drug reaction associated with long-term use of somatostatin analogues and has been frequently reported in clinical studies with pasireotide (see section ADVERSE DRUG REACTIONS). Ultrasonic examination of the gallbladder before, and at 6- to 12-month intervals during Signifor therapy is therefore recommended. The presence 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 common after trans-sphenoidal surgery and even more frequently observed post-radiation therapy of the pituitary gland. Cushing's disease patients with persistent or recurrent disease might therefore present with deficiency of one or more pituitary hormones. As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones, other than ACTH, cannot be ruled out. Therefore, monitoring of pituitary function (e.g. TSH/free T_4, GH/IGF-1) prior to initiation of therapy with Signifor and periodically during treatment should be conducted as clinically appropriate.

Drug-drug interactions

Pasireotide may decrease the relative bioavailability of cyclosporine (see section INTERACTIONS). Concomitant administration of Signifor and cyclosporine may require adjustment of the cyclosporine dose to maintain therapeutic levels of the drug.

ADVERSE DRUG REACTIONS

Summary of the safety profile

A total of 201 Cushing's disease patients received Signifor in Phase II and Phase III studies.

The safety profile of Signifor was consistent with the somatostatin analogue class, except for the occurrence of hypocortisolism and degree of hyperglycemia.

The data described below reflect exposure of 162 Cushing's disease patients to Signifor in the Phase III study. At study entry patients were randomized to receive twice a day (b.i.d.) doses of either 0.6 mg or 0.9 mg of Signifor. The mean age of patients was approximately 40 years old with a predominance of female patients (77.8%). The majority of the patients had persistent or recurrent Cushing's disease (83.3%) and few patients (≤5%) in either treatment group had received previous pituitary irradiation. The median exposure to the treatment up to the cut-off date of the primary efficacy and safety analysis was 10.37 months (0.03 to 37.8) with 67.9% of patients having at least six-months exposure.

Common Terminology Criteria for Adverse Events v.3.0 (CTC) grade 1 and 2 ADRs were reported in 57.4% of patients. CTC grade 3 ADRs were observed in 35.8% of patients and CTC grade 4 ADRs were observed in 2.5% of patients. CTC grade 3 and 4 ADRs were mostly related to hyperglycemia. The most common ADRs (incidence ≥10%) were diarrhea, nausea, abdominal pain, cholelithiasis, hyperglycemia, diabetes mellitus, fatigue and glycosylated hemoglobin increased. There were no deaths during the study. Adverse reactions reported up to the cut-off date of the analysis, suspected to be drug related by the investigators and with an overall frequency higher than 5% are presented in Table 1 by randomized dose group and overall.

Tabulated Summary of adverse drug reactions from clinical trials

ADRs from clinical trials (Table 1) are listed according to MedDRA primary System Organ Class. Within each System Organ Class, ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).

Table 1 Drug adverse reactions suspected to be drug related by the investigator with an overall frequency of more than 5% and other notable ADRs which occurred with a frequency of equal or less than 5% in the Phase III study in Cushing's disease patients

Primary System Organ Class Preferred Term	Pasireotide 0.6 mg b.i.d. N=82 n (%)	Pasireotide 0.9 mg b.i.d. N=80 n (%)	Overall N=162 n (%)	Frequency Range (Overall)
Endocrine disorders				
Adrenal insufficiency	4(4.9)	5(6.3)	9(5.6)	Common
Metabolism and nutrition disorders				
Hyperglycemia	31(37.8)	32(40.0)	63(38.9)	Very common
Diabetes mellitus	13(15.9)	16(20.0)	29(17.9)	Very common
Type 2 diabetes mellitus	10(12.2)	5(6.3)	15(9.3)	Common
Decreased appetite	6(7.3)	7(8.8)	13(8.0)	Common
Glucose tolerance impaired	2(2.4)	2(2.5)	4(2.5)	Common
Nervous system disorders				
Headache	5(6.1)	7(8.8)	12(7.4)	Common
Dizziness	3(3.8)	3(3.8)	6(3.7)	Common
Cardiac Disorders				
Sinus bradycardia	6(7.3)	1(1.3)	7(4.3)	Common
QT prolongation	3(3.7)	3(3.8)	6(3.7)	Common
Vascular disorders				
Hypotension	2(2.4)	4(5.0)	6(3.7)	Common

Blood and lymphatic system disorders				
Anemia	0(0.0)	1(1.3)	1(0.6)	Uncommon
Gastrointestinal disorders				
Diarrhea	46(56.1)	43(53.8)	89(54.9)	Very common
Nausea	33(40.2)	43(53.8)	76(46.9)	Very common
Abdominal pain	14(17.1)	19(23.8)	33(20.4)	Very common
Vomiting	2(2.4)	8(10.0)	10(6.2)	Common
Abdominal pain upper	6(7.3)	3(3.8)	9(5.6)	Common
Hepatobiliary disorders				
Cholelithiasis	25(30.5)	23(28.8)	48(29.6)	Very common
Cholecystitis[1]	4(4.9)	1(1.3)	5(3.1)	Common
Cholestasis	2(2.4)	2(2.5)	4(2.5)	Common
Skin and subcutaneous tissue disorders				
Alopecia	4(4.9)	5(6.3)	9(5.6)	Common
General disorders and administration site conditions				
Injection site reaction	10(12.2)	12(15.0)	22(13.6)	Very common
Fatigue	7(8.5)	12(15.0)	19(11.7)	Very common
Investigations				
Glycosylated hemoglobin increased	10(12.2)	7(8.8)	17(10.5)	Very common
Transaminases increased[2]	13(15.8)	8(10.0)	21(13.0)	Very common
Alanine aminotransferase increased	9(11.0)	5(6.3)	14(8.6)	Common
Aspartate aminotransferase increased	5(6.1)	3(3.8)	8(4.9)	Common
Gamma-glutamyl transferase increased	8(9.8)	7(8.8)	15(9.3)	Common
Lipase increased	7(8.5)	5(6.3)	12(7.4)	Common
Blood glucose increased	6(7.3)	3(3.8)	9(5.6)	Common
Blood amylase increased	4(4.9)	0(0.0)	4(2.5)	Common
Prothrombin time prolonged	0(0.0)	2(2.5)	2(1.2)	Common

[1]Cholecystitis includes Cholecystitis acute

[2]Transaminases increased includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma glutamyltransferase increased and Hepatic enzyme increased

Description of selected Adverse Drug Reactions

Glucose metabolism disorders

Elevated fasting plasma glucose levels was the most frequently reported CTC grade 3 laboratory abnormality (23.2% of patients) in the Phase III study in Cushing's disease patients. Mean HbA1c increases were less pronounced in patients with normal glycemia at study entry in comparison to pre-diabetic patients or diabetic patients (Table 2).

Table 2 Changes in mean HbA1c at month 6 according to glycemic status at study entry

Glycemic status at study entry	600 ug b.i.d.		900 ug b.i.d.	
(n = overall number of patients)	Baseline	Month 6	Baseline	Month 6
Normoglycemic patients (n= 62)	5.29	6.50	5.22	6.75
Pre-diabetic patients (n= 38)	5.77	7.45	5.71	7.13
Diabetic patients (n= 54)	6.50	7.95	6.42	8.30

Mean fasting plasma glucose (FPG) levels commonly increased within the first month of treatment with decreases and stabilization observed in subsequent months. Fasting plasma glucose and HbA1c values generally decreased over the 28 days following pasireotide discontinuation but remained above baseline values. Long-term follow-up data are not available. Adverse reactions of hyperglycemia and diabetes mellitus led to study discontinuation in 5 (3.1%) and 4 patients (2.5%), respectively.

Monitoring of blood glucose levels in patients treated with Signifor is recommended (see section WARNINGS AND PRECAUTIONS).

Gastrointestinal disorders
As with other somatostatin analogues, gastrointestinal disorders were frequently reported with the use of Signifor. These events were usually of low CTC grade, required no intervention and improved with continued treatment.

Injection site reactions

Injection site reactions were reported in 13.6% of patients enrolled in the Phase III trial in Cushing's disease. Injection site reactions have also been reported in clinical trials in other populations. The events were most frequently reported as local pain, erythema, hematoma, hemorrhage and pruritus. These events resolved spontaneously and required no intervention.

Thyroid function

Central hypothyroidism is a commonly described co-morbidity in Cushing's disease. Thyroid dysfunction is also a common adverse reaction associated with the use somatostatin analogs.

Hypothyroidism with the use of Signifor was reported for seven patients participating in the Phase III study in Cushing's disease, two of which were considered to be drug-related by the investigator. However, all seven patients presented with a TSH close to or below the lower limit of normal at study entry, which precludes establishing a conclusive relationship between the adverse event and the use of Signifor.

Liver enzymes

Transient elevations in liver enzymes have been reported with the use of somatostatin analogs and were also observed in healthy subjects and patients receiving pasireotide in clinical studies. The elevations were mostly asymptomatic, of low CTC grade and reversible with continued treatment. A few cases of concurrent elevations in ALT greater than 3 x ULN and bilirubin greater than 2 x ULN have been observed. All cases of concurrent elevations were identified within ten days of initiation of treatment with Signifor. The individuals recovered without clinical sequelae and liver function test results returned to baseline values after discontinuation of treatment.

Monitoring of liver enzymes is recommended prior and during treatment with Signifor (see section WARNINGS AND PRECAUTIONS), as clinically appropriate.

Pancreatic enzymes

Asymptomatic elevations in lipase and amylase have been observed in patients receiving pasireotide in clinical studies. The elevations were mostly low CTC grade and reversible while continuing treatment. Pancreatitis is a potential adverse reaction associated with the use of somatostatin analogs due to the association between choletithiasis and acute pancreatitis.

INTERACTIONS

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

Anticipated pharmacokinetic interactions resulting in effects on pasireotide

In vitro, pasireotide has been shown to be a P-gp substrate. There is potential for strong P-gp inhibitors, e.g. ketoconazole, ciclosporin, verapamil, clarithromycin, to increase concentrations of pasireotide but the clinical implications of this potential effect are not known.

Anticipated pharmacokinetic interactions resulting in effects on other medicinal products

Pasireotide may decrease the relative bioavailability of ciclosporin. Concomitant administration of pasireotide and ciclosporin may require adjustment of the ciclosporin dose to maintain therapeutic levels.

Anticipated pharmacodynamic interactions

Medicinal products that prolong the QT interval

Pasireotide should be used with caution in patients who are concomitantly receiving medicinal products that prolong the QT interval, such as class Ia antiarrhythmics (e.g. quinidine, procainamide, disopyramide), class III antiarrhythmics (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide), certain antibacterials (intravenous erythromycin, pentamidine injection, clarithromycin, moxifloxacin), certain antipsychotics (e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone), certain antihistamines (e.g. terfenadine, astemizole, mizolastine), antimalarials (e.g. chloroquine, halofantrine, lumefantrine), certain antifungals (ketoconazole, except in shampoo) (see also section WARNINGS AND PRECAUTIONS).

Bradycardic medicinal products

Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving pasireotide concomitantly with bradycardic medicinal products, such as beta blockers (e.g. metoprolol, carteolol, propranolol, sotalol), acetylcholinesterase inhibitors (e.g. rivastigmine, physostigmine), certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil), certain antiarrhythmics (see also section WARNINGS AND PRECAUTIONS).

Insulin and antidiabetic medicinal products

Dose adjustments (decrease or increase) of insulin and antidiabetic medicinal products (e.g. metformin, liraglutide, vildagliptin, nateglinide) may be required when administered concomitantly with pasireotide (see also section WARNINGS AND PRECAUTIONS).

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential and contraceptive measures

Animal studies have shown pasireotide to be harmful to the developing fetus. Women of child- bearing potential are recommended to use effective contraception during treatment with pasireotide, and should also be advised that treatment with pasireotide may lead to improved fertility (see sub-section 'Fertility').

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity (see section NON-CLINICAL SAFETY DATA). The potential risk for humans is not known. Signifor should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Labor and delivery

No data in humans are available. Studies in rats have shown no effects on labour and delivery (see section NON-CLINICAL SAFETY DATA).

Breast-feeding

It is not known whether pasireotide is excreted in human milk. Available data in rats with pasireotide via the s.c. route have shown excretion of pasireotide in milk (see section NON-CLINICAL SAFETY DATA). As a risk to the breastfed child cannot be excluded, Signifor should not be used by the nursing mother.

Fertility

Studies in rats with pasireotide via the s.c. route have shown effects on female reproductive parameters (see section NON-CLINICAL SAFETY DATA). The clinical relevance of these effects in humans is unknown.

The therapeutic benefits of a reduction or normalization of serum cortisol levels in female patients with Cushing's disease treated with pasireotide may lead to improved fertility.

OVERDOSAGE

No cases of overdosage have been reported in patients receiving pasireotide subcutaneously. Doses up to 2.1 mg twice a day have been used in healthy volunteers with adverse reactions of diarrhea being observed at a high frequency.

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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Pasireotide is a novel cyclohexapeptide, injectable somatostatin analogue. Like natural peptide hormones somatostatin-14 and somatostatin-28 (also known as Somatotropin Release Inhibiting Factor [SRIF]) and other somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTR). Five human somatostatin receptor subtypes are known: (SSTR) 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Pasireotide binds with high affinity to four of the five SSTRs. The binding affinities of endogenous somatostatin and pasireotide are shown in Table 3.

Table 3 Binding affinities of somatostatin (SRIF-14) and pasireotide to the five human SSTR receptor subtypes (SSTR1-5)

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	> 100	0.16±0.01

Results are the mean±SEM of IC_{50} values expressed as nmol/L (nM).

Pharmacodynamics (PD)

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumors where hormones are excessively secreted including adrenocorticotropic hormone (ACTH) in Cushing's disease. *In vitro* studies have shown that corticotroph tumor cells from Cushing's disease patients display a high expression of hsst5 whereas the 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. The high affinity of pasireotide for four of the five hssts, especially to hsst5 (see Table 3), provides the basis for pasireotide to be an effective treatment for Cushing's disease patients.

Glucose metabolism

In a randomized double-blinded mechanism study conducted in healthy volunteers, the development of hyperglycemia with pasireotide administered as Signifor s.c. at doses of 600 and 900 microgram twice a day was related to significant decreases in insulin secretion as well as incretin hormones (i.e. Glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). Pasireotide did not affect insulin sensitivity. In another randomized study conducted in healthy volunteers, the effects of pasireotide on blood glucose were investigated by comparison between administrations of Signifor s.c. 600 microgram twice a day alone and with co-administration of an anti-hyperglycemic drug (metformin, nateglinide, vildagliptin or liralgutide, respectively. Insulin was not studied) over a 7-day period. Incretin-based therapy (GLP-1 agonists and DDP-IV inhibitors) was most efficacious in treating pasireotide-associated hyperglycemia in healthy volunteers.

Cardiac Electrophysiology

The effect of pasireotide (administered as Signifor s.c.) on the QT interval was assessed in two open-label, controlled, cross-over thorough QT studies. In the first study that investigated a dose of 1950ug administered twice a day, the maximum mean placebo-subtracted QTcF change from baseline (ΔΔQTcI) was 17.5 ms (90%CI: 15.53; 19.38). In the second study, that investigated doses of 600 ug and 1950ug twice a day, the maximum mean placebo-subtracted

QTcI changes from baseline (ΔΔQTcI) were 13.19 ms (90%CI: 11.38; 15.01) and 16.12 ms (90%CI: 14.30; 17.95 ms), respectively. In both studies the maximum placebo-subtracted mean change from baseline occurred at 2 hours post dose. Both Signifor doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for the dose of 600 ug twice a day (-10.39 bpm), and at 0.5 hours for the dose of 1950 ug twice a day (-14.91 bpm). No episodes of torsade de pointes were observed(see section WARNING AND PRECAUTIONS).

The increase in QT interval with administration of pasireotide is not mediated by an effect on the hERG potassium channel. Cardiac restitution, the ability of the heart to recover from each preceding beat, was measured on continuous 24-hour ECGs to determine the effect of pasireotide on arrhythmia vulnerability. Pasireotide significantly improved all restitution parameters in the presence of QT prolongation indicating that pasireotide mediated QT prolongation may not be associated with an increased pro-arrhythmic risk. Further, quantitative T wave morphological analysis showed no changes indicative of impaired spatial heterogeneity of cardiac repolarization during pasireotide treatment.

Pharmacokinetics (PK)

In healthy volunteers, pasireotide demonstrates approximately linear pharmacokinetics (PK) for a wide dose range from 0.0025 to 1.5mg single dose. In Cushing's disease patients, pasireotide demonstrates linear dose-exposure relationship in a dose range from 0.3 to 1.2mg b.i.d. doses.

Absorption

In healthy volunteers, pasireotide s.c. is rapidly absorbed and peak plasma concentration is reached within T_{max} 0.25-0.5 hour. C_{max} and AUC are approximately dose-proportional following administration of single and multiple doses.

No studies have been conducted to evaluate the bioavailability of pasireotide in humans.

Food effect is unlikely to occur since Signifor is administered via parenteral route.

Distribution

In healthy volunteers, pasireotide is widely distributed with large apparent volume of distribution (V_z/F >100 L). Distribution between blood and plasma is concentration independent and shows that pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

Pasireotide has low passive permeability and is likely to be a substrate of P-gp, but the impact of P-gp on ADME (absorption, distribution, metabolism, excretion) of pasireotide is expected to be low. Based on *in vitro* data, at therapeutic dose levels, pasireotide is not a substrate of the efflux transporter BCRP (breast cancer resistance protein), nor of the influx transporters OCT1 (organic cation transporter 1), OATP (organic anion-transporting polypeptides) 1B1, 1B3, or 2B1. At therapeutic dose levels pasireotide is also not an inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1), OATP1B1 or 1B3, P-gp, BCRP, MRP2 (multiresistance protein 2) and BSEP (bile salt export pump).

Biotransformation/metabolism

Pasireotide was shown to be highly metabolically stable in human liver and kidney microsomes. In healthy volunteers, pasireotide in its unchanged form is the predominant form

found in plasma, urine and feces.

Elimination

Pasireotide s.c. is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route. In a human ADME study with pasireotide s.c. administered as with a single dose of 600 microgram 55.9 ± 6.63% of the radioactivity dose was recovered over the first 10 days post dosing, including 48.3 ± 8.16% of the radioactivity in feces and 7.63 ± 2.03% in urine.

The clearance (CL/F) of pasireotide in healthy volunteers and Cushing's disease patients is ~7.6 liters/h and ~3.8 liters/h respectively.

Steady-state pharmacokinetics

Following multiple s.c. doses, pasireotide demonstrates linear and time-independent pharmacokinetics in the dose range of 0.05 to 0.6 mg once a day (q.d.) in healthy volunteers, and 0.3 mg to 1.2 mg twice a day in Cushing's disease patients. Based on the accumulation ratios of AUC, the calculated effective half-life ($t_{1/2,eff}$) in healthy volunteers was approximately 12 hours (on average between 10 and 13 hours for 0.05, 0.2 and 0.6mg q.d. doses) (see section DOSAGE AND ADMINISTRATION).

Special populations

Geriatric patients (65 years of age or older)

Age has been found to be a covariate in the population PK analysis of Cushing's disease patients. Decreased total body clearance and increased PK exposures have been seen with increasing age. In the studied age range 18 to 73 years, the area under the curve at steady state for one dosing interval of 12 hours (AUC_{ss}) is predicted to range from 86% to 110% of that of the typical patient of 41 years. This variation is moderate and considered of minor significance considering the wide age range in which the effect was observed.

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

Pediatric patients

No studies have been performed in pediatric patients.

Patients with renal impairment

Renal clearance has a minor contribution to the elimination of pasireotide in humans.

In a clinical study [55] with single dose administration of 900 micrograms pasireotide as Signifor s.c. in subjects with impaired renal function, renal impairment of mild, moderate or severe degree or end stage renal failure did not have a significant impact on the pharmacokinetics of pasireotide.

Patients with hepatic impairment

In a clinical study with single dose administration of 600 micrograms pasireotide administered as Signifor s.c in subjects with impaired hepatic function (Child-Pugh A, B and C), subjects

with moderate and severe hepatic impairment (Child-Pugh B and C) showed significantly higher exposures than subjects with normal hepatic function. Upon correction for covariate effect (age, BMI and albumin)AUC_{inf} was increased by 60% and 79%, C_{max} increased by 67% and 69%, and CL/F decreased by 37% and 44%, respectively, in the moderate and severe hepatic impairment groups relative to the control group.

Demographics

Population PK analyses of pasireotide (administered as Signifor s.c.) suggest that race and gender, do not influence PK parameters.

Lean body weight, which subtracts the estimated weight of body fat from the total body weight, has been found to be a covariate in the population PK analysis of Cushing's disease patients. In the studied lean body weight range 33 to 83 kg, the AUC_S is predicted to range from 67% to 134% of that of the typical patient of 49 kg (The corresponding range of total body weight was 43.0 to 175 kg, with a median of 77.4 kg). This variation is considered as moderate and of minor clinical significance.

CLINICAL STUDIES

A phase III, multicentre, randomised study was conducted to evaluate the safety and efficacy of different dose levels of Signifor over a twelve-month treatment period in Cushing's disease patients with persistent or recurrent disease or *de novo* patients for whom surgery was not indicated or who refused surgery.

The study enrolled 162 patients with a baseline UFC >1.5 x ULN who were randomised in a 1:1 ratio to receive a subcutaneous dose of either 0.6 mg s.c. twice a day or 0.9 mg twice a day of Signifor. After three months of treatment, patients with a mean 24-hour UFC ≤2 x ULN and below or equal to their baseline value continued blinded treatment at the randomised dose until month 6. Patients who did not meet these criteria were unblinded and the dose was increased by 0.3 mg twice a day. After the initial 6 months in the study, patients entered an additional 6-month open-label treatment period. If response was not achieved at month 6 or if the response was not maintained during the open-label treatment period, dosage could be increased by 0.3 mg s.c. twice a day. The dose could be reduced by decrements of 0.3 mg twice daily at any time during the study for reasons of intolerability. The primary efficacy end-point was the proportion of patients in each arm who achieved normalisation of mean 24-hour UFC levels (UFC ≤ULN) after 6 months of treatment and who did not have a dose increase (relative to randomised dose) during this period. Secondary end-points included, among others, changes from baseline in: 24-hour UFC, plasma ACTH, serum cortisol levels, and clinical signs and symptoms of Cushing's disease. All analyses were conducted based on the randomised dose groups.

Baseline demographics were well balanced between the two randomised dose groups and consistent with the epidemiology of the disease. The mean age of patients was approximately 40 years and the majority of patients (77.8%) were female. Most patients (83.3%) had persistent or recurrent Cushing's disease and few (≤5%) in either treatment group had received previous pituitary irradiation.

Baseline characteristics were balanced between the two randomised dose groups, except for marked differences in the mean value of baseline 24-hour UFC (1156 nmol/24 h for the 0.6 mg twice a day group and 782 nmol/24 h for the 0.9 mg twice a day group; normal range 30-145 nmol/24 h).

Results

At month 6, normalisation of mean UFC levels was observed in 14.6% (95% CI 7.0-22.3) and 26.3% (95% CI 16.6-35.9) of patients randomised to pasireotide 0.6 mg and 0.9 mg twice a day, respectively. The study met the primary efficacy objective for the 0.9 mg twice a day group as the lower limit of the 95% CI is greater than the pre-specified 15% boundary. The response in the 0.9 mg dose arm seemed to be higher for patients with lower mean UFC at baseline. The responder rate at month 12 was comparable to month 6, with 13.4% and 25.0% in the 0.6 mg and 0.9 mg twice a day groups, respectively.

A supportive efficacy analysis was conducted in which patients were further classified into 3 response categories regardless of up-titration at month 3: controlled (UFC ≤1.0 x ULN), partially controlled (UFC >1.0 x ULN but with a reduction in UFC ≥50% compared to baseline) or uncontrolled (all other patients). The controlled and partially controlled responder rates at month 6, constituted 34% and 41% (0.6 mg twice a day and 0.9 mg twice a day, respectively) of the randomized patients (Table 5). Patients uncontrolled at both Months 1 and 2 were likely (90%) to remain uncontrolled at Months 6 and 12.

In both dose groups, Signifor resulted in a decrease in mean UFC after 1 month of treatment which was maintained over time.

Decreases were also demonstrated by the overall percentage of change in mean and median UFC levels at month 6 and 12 as compared to baseline values (see Table 4). Reductions in plasma ACTH levels were also observed at each time point for each dose group.

Table 4 Percentage change in mean and median UFC levels per randomized dose group at Month 6 and month 12 compared to baseline values

		Pasireotide 0.6 mg b.i.d. % change (n)	Pasireotide 0.9 mg b.i.d. % change (n)
Mean change in UFC (% from baseline)	Month 6	-27.5* (52)	-48.4 (51)
	Month 12	-41.3 (37)	-54.5 (35)
Median change in UFC (% from baseline)	Month 6	-47.9 (52)	-47.9 (51)
	Month 12	-67.6 (37)	-62.4 (35)

Decreases in sitting systolic and diastolic blood pressure, body mass index (BMI) and total cholesterol were observed in both dose groups at month 6. Overall reductions in these parameters were observed in patients with full and partial mean UFC control but tended to be greater in patients with normalised UFC. Similar trends were observed at month 12.

NON-CLINICAL SAFETY DATA

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction and development. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. Effects in non-clinical studies were observed at exposures considered similar to or in excess of the maximum human exposure. Pasireotide was not genotoxic in *in vitro* and *in vivo* assays.

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

carcinogenic potential.

Pasireotide did not affect fertility in male rats but, as expected from the pharmacology of pasireotide, females presented abnormal cycles or acyclicity, and decreased numbers of corpora lutea and implantation sites. Embryo toxicity was seen in rats and rabbits at doses that caused maternal toxicity but no teratogenic potential was detected. In the pre- and postnatal study in rats, pasireotide had no effects on labour and delivery, but caused slight retardation in the development of pinna detachment and reduced body weight of the offspring.

Available toxicological data in animals have shown excretion of pasireotide in milk.

INCOMPATIBILITIES

No compatibility data with other products have been generated. Pasireotide solution for injection is to be used without any dilution and must not to be mixed with other medicinal products.

STORAGE

See folding box.

Signifor should not be used after the date marked "EXP" on the pack.

Signifor must be kept out of the reach and sight of children.

DOSAGE FORMS OR PRESENTATION

One-point-cut colourless, type I glass ampoule containing 1 ml of solution.

Each ampoule is packed in a cardboard tray which is placed in an outer box.

Packs containing 6 ampoules or multipacks containing 30 (5 packs of 6) or 60 (10 packs of 6) ampoules.

Not all pack sizes may be marketed.

INSTRUCTIONS FOR USE AND HANDLING

The solution for injection is supplied in a 1 ml one point-cut colorless hydrolytic class I (Ph. Eur., USP) glass ampule i.e. a small glass container.

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

To ensure proper administration of the drug, the patient should be instructed by a physician or other health care professional how to use the Signifor ampule.

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

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

Store Signifor 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 long thick blunt sterile needle for drawing up the solution (your doctor or nurse will tell you if this is needed)
5. One short fine sterile needle
6. A sharps container or other rigid closed disposal container

The injection site

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

Getting started

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

- Wash your hands thoroughly with soap and water.
- 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 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.

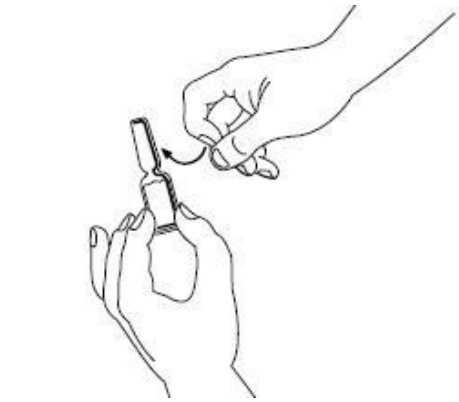
Ampoules should be opened just prior to administration, and any unused portion discarded.

Check the expiry date and the dose:

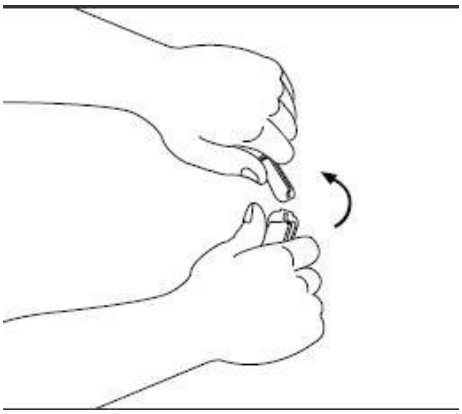
Check the expiry date (EXP) which is stated on the ampule label and check that it is the dose your doctor has prescribed for you.

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.

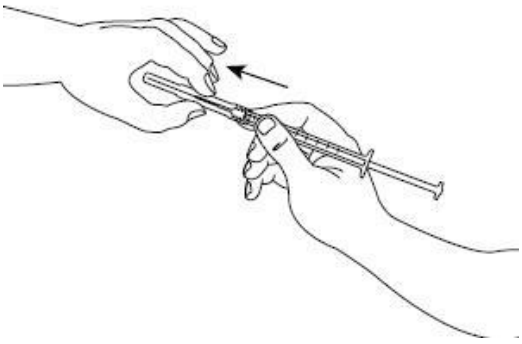
How to inject Signifor



Step 1: Signifor solution for injection is filled in a break-off ampule. The colored dot on the top part marks the position of the breaking cut on the neck of the ampule. Tap the ampule with your finger in order to make sure there is no liquid in the top part when you open the ampule.

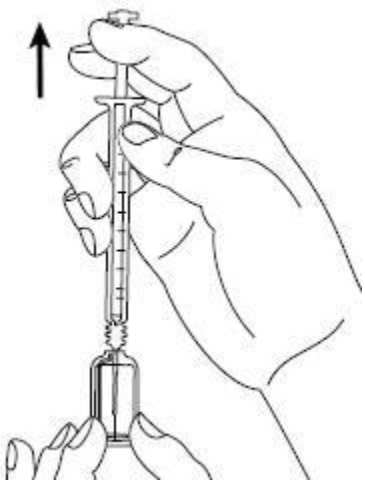


Step 2: Recommended procedure: hold the ampule in an upright position with the colored dot facing away from you. Hold the base of the ampule in one hand. Keeping your thumbs together above and below the neck, break off the top of the ampule at the breaking cut. Once open, put the ampule upright on a clean, flat surface.

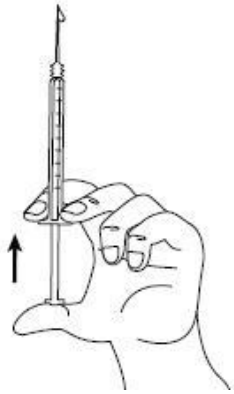


Step 3: Take the sterile syringe and attach the needle to it. If you have been told to use two needles, you should use the long thick blunt one for this step.

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

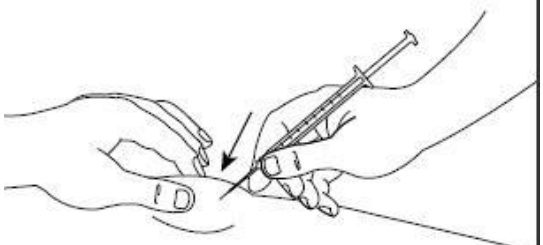


Step 4: Remove the cover from the needle. Put the needle into the ampule and pull the plunger to draw the entire contents of the ampule into the syringe. If you have been told to use two needles, you should now replace the long needle with the short one.



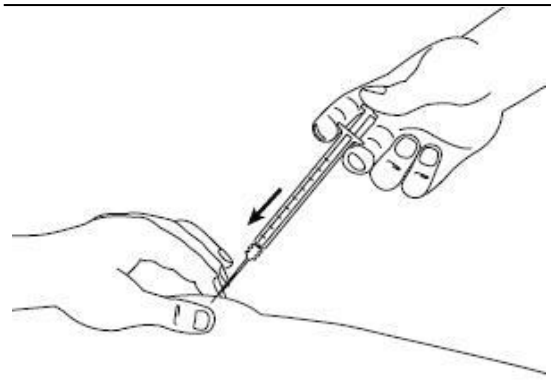
Step 5: Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger. Tap the syringe with your fingers to get rid of air bubbles. Make sure there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.

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

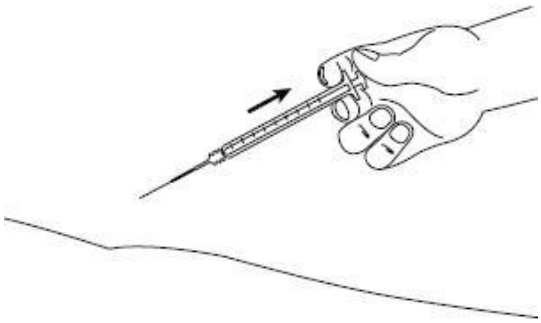


Step 6: Gently pinch the skin at the injection site and, holding the needle at an angle of approximately 45 degrees (as shown in the picture) insert it into the injection site.

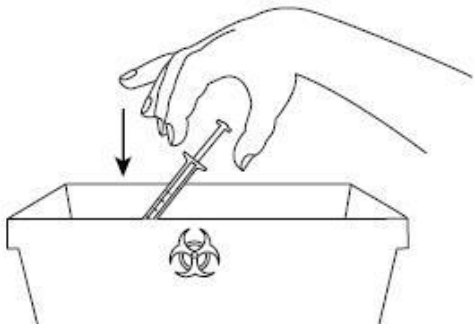
Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, first remove the needle from the skin, then replace the short needle with a new one and insert it into a different injection site.



Step 7: Always keeping your skin pinched, slowly press 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:

See folding box.

International Package Leaflet

Information issued: December 2016.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland