NOVARTIS

For the use of only Registered Medical Practitioners or a Hospital or a Laboratory.

Pasireotide solution for injection

Signifor®

0.3mg/ml, 0.6mg/ml, 0.9mg/ml solution for injection

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, tartaric acid, sodium hydroxide, water for injections.

INDICATIONS

Treatment of patients with Cushing's disease for whom medical therapy is appropriate

DOSAGE AND ADMINISTRATION

Dosage

General target population

Adults

The recommended initial dose of Signifor is 0.9 mg by subcutaneous (s.c.) injection twice a day. For patients with pre-diabetes or diabetes mellitus an initial dose of 0.6 mg twice a day may be considered (see section WARNINGS AND PRECAUTIONS).

Management of suspected adverse reactions may require temporary dose reduction of Signifor. Dose reduction by decrements of 0.3 mg twice a day is suggested.

After two months of initiating treatment with Signifor patients should be evaluated for clinical benefit. Patients who experience clinical benefit (clinically meaningful reduction in Urinary Free Cortisol [UFC] levels and/or improvement in signs or symptoms of the disease) should continue therapy with Signifor as long as benefit is derived. Patients who do not experience clinical benefit from Signifor should be considered for discontinuation.

Individualized dose reduction may be considered for patients with a stable response at the discretion of the treating physician.

Special populations

Patients with renal impairment

No dosage 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). The recommended initial dose for patients with moderately impaired hepatic function (Child-Pugh B) is 0.3 mg twice a day (see section CLINICAL PHARMACOLOGY). The maximum recommended dose for patients with moderate hepatic impairment 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.

Elderly patients

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).

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

As with other somatostatin analogues, 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 DRUGS REACTIONS).

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. In the majority of patients who developed hyperglycemia, the condition appeared to be manageable with appropriate antidiabetic therapy. Dose reductions or discontinuation of treatment with pasireotide due to hyperglycemia were infrequent.

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 every week for the first two to three months and periodically thereafter, as clinically appropriate. 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 hyperglycaemia. 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.

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 has been shown to prolong the QT interval on the ECG in two healthy volunteer studies (see section CLINICAL PHARMACOLOGY). The clinical significance of this prolongation is unknown.

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 torsade de pointes were not observed either in those studies or in clinical studies in other patient populations.

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,
- with hypokalemia and/or hypomagnesemia.

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

Liver tests

Mild transient elevations in aminotransferases have been 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 after 2 to 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.

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, can not 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

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.

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.

The frequency and severity of adverse drug reactions (ADRs) was comparable between the two dose groups. Grade 1 and 2 ADRs were reported in 57.4% of patients. Grade 3 ADRs were observed in 35.8% of patients and Grade 4 ADRs were observed in 2.5% of patients. 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.

ADRs 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. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).

Table 1 **Drug adverse reactions with an overall frequency of more 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

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)
Decreased appetite	6(7.3)	7(8.8)	13(8.0)	Common
Nervous system disorders				
Headache	5(6.1)	7(8.8)	12(7.4)	Common
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
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
Gamma-glutamyltransferase increased	8(9.8)	7(8.8)	15(9.3)	Common
Alanine aminotransferase increased	9(11.0)	5(6.3)	14(8.6)	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

Other notable ADRs which occurred with a frequency less than 5% were:

Cardiac disorders

Common: Sinus bradycardia (overall 4.3%); QT prolongation (overall 3.7%)

Vascular disorders

Common: Hypotension (overall 3.7%)

Blood and lymphatic disorders

Uncommon: Anemia (overall: 0.6%)

Investigations

Common: Blood amylase increased (overall 2.5%) and Prothrombin time prolonged (overall: 1.2%).

Description of selected ADRs

Glucose metabolism disorders

Elevated glucose was the most frequently reported 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 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 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 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.

Pasireotide has moderate protein binding and is metabolically highly stable. Pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein) but is not an inhibitor or inducer of P-gp. In addition, at therapeutic dose levels, pasireotide is not expected to be:

- a substrate, inhibitor or inducer of any major enzymes of CYP450;
- a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1) and OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1;
- an inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1, influx transporter OATP 1B1 or 1B3, efflux transporter MRP2 (multiresistance protein 2) or BSEP (bile salt export pump).

Based on all these *in vitro* data, the potential for protein binding, metabolism and/or transporter mediated DDI is low between pasireotide and co-medications *in vivo*.

Caution is required when co-administering Signifor with anti-arrhythmic medicines and other drugs that may prolong the QT interval (See Section WARNINGS AND PRECAUTIONS).

Anticipated interactions resulting in effects on other drugs

Limited published data suggest that somatostatin analogs might have an indirect effect in decreasing the metabolic clearance of compounds metabolized by CYP450 enzymes, via suppression of growth hormone secretion. The possibility that pasireotide may exert such an indirect effect can not be excluded based on available data. Caution should be exercized when administering pasireotide concomitantly with drugs possessing a low therapeutic index and which are metabolized mainly by CYP3A4 (e.g. quinidine, terfenadine).

In dogs, pasireotide has been found to decrease blood level of cyclosporine by reducing its intestinal absorption. It is unknown whether such interaction occurs in humans. Therefore dose adjustments of cyclosporine may be required when co-administering pasireotide and cyclosporine (see section WARNINGS AND PRECAUTIONS).

Limited data with other somatostatin analogues suggest that co-administration with bromocriptine may increase the availability of bromocriptine. Available data can not exclude the possibility that pasireotide may exert such an effect.

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

Labour 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).

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 only be prescribed to pregnant women under compelling circumstances.

Breast-feeding

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

Fertility

It is unknown whether pasireotide has an effect on human fertility. Studies in rats have shown effects on female reproductive parameters (see section NON-CLINICAL SAFETY DATA).

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

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. Five human somatostatin receptor subtypes are known: hsst 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogues bind to hsst receptors with different potencies (Table 3). Pasireotide binds with high affinity to four of the five hssts.

Table 3 **Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and lanreotide to the five human sst receptor subtypes (hsst1-5)**

Compound	hsst1	hsst2	hsst3	hsst4	hsst5
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	> 1000	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

Results are the mean+SEM of IC_{50} values expressed as nmol/L.

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. Due to its broad binding profile to somatostatin receptors, pasireotide has the potential to treat diseases characterized by expression of those receptors in the target tissues.

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.

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 QTc interval was observed with the maximum placebo-subtracted mean change from baseline occurring at 2h post dose. In one of the studies investigating a 1950ug b.i.d. dose, the maximum mean placebo-subtracted QTcF change from baseline was 17.5 ms (90%CI: 15.53; 19.38). In the other study, investigating doses of 600 ug b.i.d. and 1950ug b.i.d., the maximum mean placebo-subtracted QTcI change from baseline was 13.19 ms (90%CI: 11.38; 15.01) and 16.12 ms (90%CI: 14.30; 17.95 ms), respectively. Both pasireotide doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for pasireotide 600 µg bid (-10.39 bpm), and at 0.5 hours for pasireotide 1950 µg bid (-14.91 bpm). No episodes of torsade de pointes (transient or sustained) were observed.

Pharmacokinetics (PK)

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

Absorption

In healthy volunteers, pasireotide 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. Based on data of absolute bioavailability from pre-clinical studies in rats and monkeys, the absolute bioavailability of pasireotide s.c. is predicted to be complete 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. Pasireotide is not a substrate of BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), nor OATP (organic anion-transporting polypeptides) 1B1, 1B3, or 2B1.

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.

Excretion

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route. In a human ADME study 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 ~6.7 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).

Special populations

Elderly patients

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

Clinical studies have not been performed in patients with impaired renal function. However, renal clearance has a minor contribution to the elimination of pasireotide in humans. Renal function is not expected to significantly impact the circulating levels of pasireotide.

Patients with hepatic impairment

In a clinical study 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 Signifor 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, multicenter, randomized 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 randomized in a 1:1 ratio to receive a dose of either 0.6 mg s.c. b.i.d. or 0.9 mg s.c. b.i.d. of Signifor. After three months of treatment patients who had a mean 24-hour UFC ≤2xULN and below or equal to their baseline values 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 b.i.d. 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 the response was not maintained during the open-label treatment period dosage could be increased by 0.3 mg s.c. b.i.d. The maximum dose administered to patients was 1.2 mg s.c b.i.d. The dose could be reduced by 0.3 mg b.i.d. decrements at any time during the study for intolerability.

The primary efficacy end-point was the proportion of patients in each arm who achieved normalization of mean 24-hour UFC levels (UFC ≤ ULN) after 6 months of treatment and who did not have a dose increase (relative to randomized dose) during this period. Secondary end-points included, among others, 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 conducted based on the randomized dose groups.

Baseline demographics were well balanced between the two randomized dose groups and consistent with the epidemiology of the disease. 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.

Baseline characteristics were balanced between the two randomized dose groups, except for marked differences in the mean value of the baseline 24-hour UFC (1,156 nmol/24hr for the 0.6 mg b.i.d. group and 781 nmol/24hr for the 0.9 mg b.i.d. group); normal range 30 to 145 nmol/24 hr).

Results

At month 6, 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 randomized to pasireotide 0.6 mg b.i.d. and 0.9 mg b.i.d., respectively. The study met the primary efficacy objective for the 0.9 mg b.i.d. 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 (Table 4). The majority of responders (55.6%) at month 6 were also responders at month 12. The responder rate at month 12 was comparable to month 6 with 13.4% and 25.0% in the 0.6 mg b.i.d. and 0.9 mg b.i.d., respectively.

Table 4 **Response rates at month 6 per randomized dose group and according to baseline mean UFC – Primary efficacy analysis**

	Pasireotide 0.6 mg b.i.d.	Pasireotide 0.9 mg b.i.d.
Baseline mUFC category	n/N (%) 95% CI	n/N (%) 95% CI
>ULN to ≤2 x ULN	1/ 12 (8.3) (0.0, 24.0)	7/ 14 (50.0) (23.8, 76.2)
>2 x ULN to ≤5 x ULN	7/ 26 (26.9) (9.9, 44.0)	10/ 40 (25.0) (11.6, 38.4)
>5 x ULN to ≤10 x ULN	3/ 28 (10.7) (0.0, 22.2)	1/ 13 (7.7) (0.0, 22.2)

>10 x ULN	1/ 11 (9.1) (0.0, 26.1)	0/ 9 (0.0) N/A
Unavailable*	0/ 5 (0.0) N/A	3/ 4 (75.0) (32.6, 100.0)

* Patients with less than the minimum required three UFC samples at baseline for the calculation of mUFC.

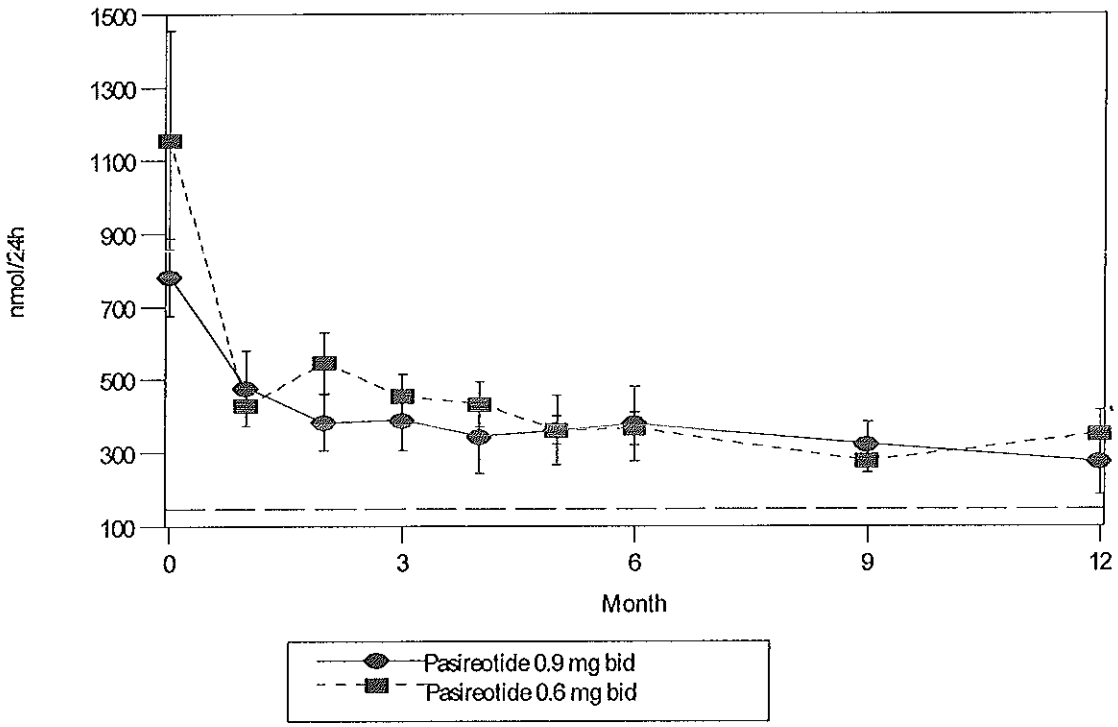
A supportive efficacy analysis was conducted in which patients were further classified into 3 response categories regardless of up-titration at month 3: controlled (UFC ≤1.0 x ULN), partially controlled (UFC >1.0 x ULN but with a reduction in UFC ≥50% compared to baseline) or uncontrolled (all other patients). The controlled and partially controlled responder rates at month 6, constituted 34% and 41% (0.6 mg b.i.d and 0.9 mg b.i.d, 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.

Table 5 Response rates at month 6 per randomized dose group - supportive efficacy analysis

Response category	Pasireotide 0.6 mg b.i.d. (N=82) n (%)	Pasireotide 0.9 mg b.i.d.(N=80) n (%)
Controlled	13 (15.9%)	23 (28.8%)
Partially controlled	15 (18.3%)	10 (12.5%)
Uncontrolled	54 (66 %)	47 (59%)

In both dose groups, Signifor resulted in a rapid and robust decrease in the mean UFC after 1 month of treatment which was maintained over time (Figure 1). Dose decreases and increases appeared to have minimal effect on UFC response, though some patients experienced further reduction in UFC levels with dose up-titration.

Figure 1 Mean (±SE) Urinary Free Cortisol (nmol/24h) at time points up to Month 12 by randomized dose group



Note: Patients were randomized to Signifor 0.6 mg or 0.9 mg bid at baseline. At least three 24h UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12. At least two 24h UFC assays contributed to patient mean results at other time points. The reference line is the upper limit normal for UFC, which is 145 nmol/24h.
+/-Standard errors are displayed.

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

Table 6 **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)

* Includes one patient with significant outlying results who had a percent change from baseline of +542.2%.

Clinically meaningful decreases in sitting systolic and diastolic blood pressure, BMI, and total cholesterol were observed in both dose groups at month 6. Overall reductions in these parameters tended to be greater in patients that normalized UFC. Similar trends were observed at month 12, with the addition of serum triglycerides also decreasing at that time point. No clinically meaningful changes in bone mineral density were observed.

There were favorable shifts in all of the studied signs of Cushing's disease in both dose groups at month 6. Facial rubor improved in 36.7% (18/49) and 59.6% (28/47) of patients treated with 0.6 and 0.9 mg b.i.d., respectively. More than a third of patients in either treatment group also demonstrated improvement in supraclavicular fat pad and dorsal fat pad. Similar findings were recorded at the Month 12 visit.

Baseline mean and median global CushingQoL scores were similar for the two dose groups. At the Month 3 visit, patients in both dose groups reported increases in scores, indicating improvement in the patient-reported HRQL. At month 6, median improvements from baseline were 13.2% and 30% in the 0.6 mg and 0.9 mg b.i.d dose groups, respectively. At month 12, median improvements from baseline were 26% and 20.6% in the 0.6 mg and 0.9 mg b.i.d dose groups, respectively.

NON-CLINICAL SAFETY DATA

Non-clinical safety studies included 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 only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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

Pasireotide was not genotoxic in a battery of *in vitro* assays (Ames mutation test in Salmonella and E coli. and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an *in vivo* rat bone marrow nucleus test at doses up to 50 mg/kg, approximately 250 fold the maximum recommended therapeutic human dose (MHRD) based on surface area, mg/m^2.

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 (respectively 10 and 5 mg/kg/day) leading to exposures (AUC 0 to 24 hrs) respectively 145- and 40-fold higher than the MHRD. 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, 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-fold MHRD). Pasireotide had no effects on labour and delivery in rats administered up to 10 mg/kg/day (52-fold higher than the MHRD based on surface area, mg/m^2). Available toxicological data in animals have shown excretion of pasireotide in milk. Retardation of physiological growth, attributed to GH inhibition was observed at 2 mg/kg/day (10-fold higher than the MHRD based on surface area, mg/m^2) during a pre- and postnatal study in rats. After weaning, body weight gains in the rat pups exposed to pasireotide were comparable to controls, showing reversibility. Pasireotide did not affect fertility in male rats at doses up to 10 mg/kg/day (a dose 52-fold higher than the MHRD based on surface area, mg/m^2). In female rats, as expected from the pharmacology of pasireotide, fertility was decreased at daily doses of 0.1 mg/kg/day (0.6-fold the maximum recommended therapeutic human dose based on surface area, mg/m^2) as shown by decreased numbers of corpora lutea and implantation sites. Abnormal cycles or acyclicity were

observed at 1 mg/kg/day (5-fold higher than the MHRD based on surface area, mg/m^2).

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.

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.

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

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

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:

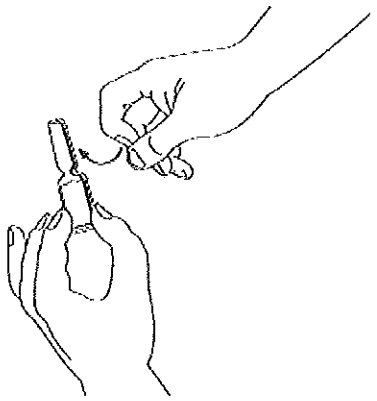
- Wash your hands thoroughly with soap and water.
- Always use a new disposable needle and syringe every time you give yourself an injection.
- Use syringes and needles only once. **Never** share needles and syringes with someone else.
- Take the ampule out of the box.
- Carefully inspect the ampule.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

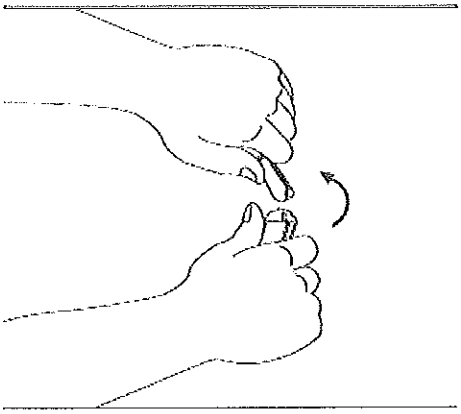
DO NOT USE if the medicine has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

How to inject Signifor

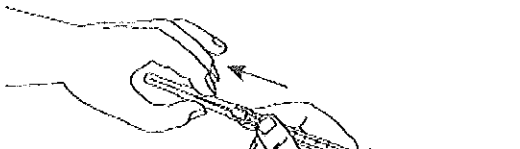


Before you proceed to Step 1, clean the injection site you have selected with an alcohol swab.

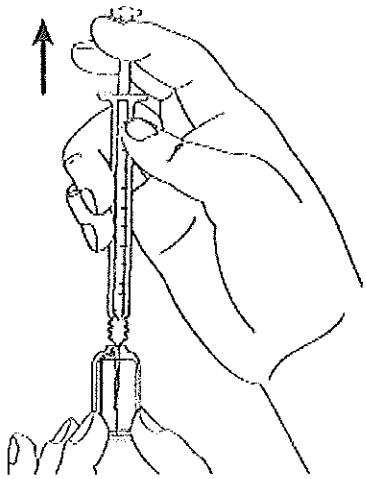
Step 1: Signifor solution for injection is filled in a snap-off ampule. Tap the ampule with your finger in order to make sure there is no liquid in the lid when you open the ampule.



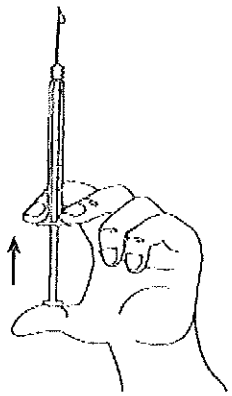
Step 2: Open it by snapping off the top of the ampule at the line marked on the ampule neck. Once open, put the ampule upright on a clean, flat surface.



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

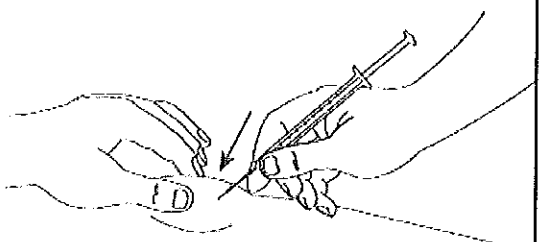


Step 4: Put the needle into the ampule and pull the plunger to draw the entire contents of the ampule into the syringe.



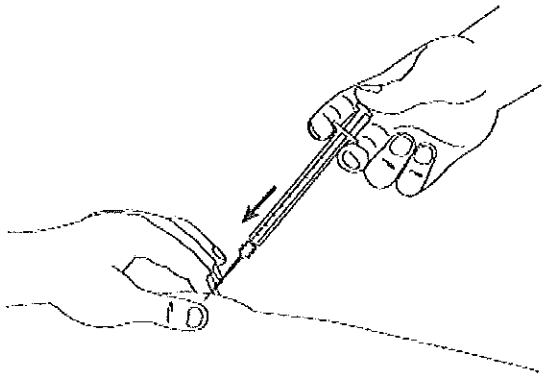
Step 5: Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger. Tap the syringe with your fingers to get rid of air bubbles. Make sure there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.

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



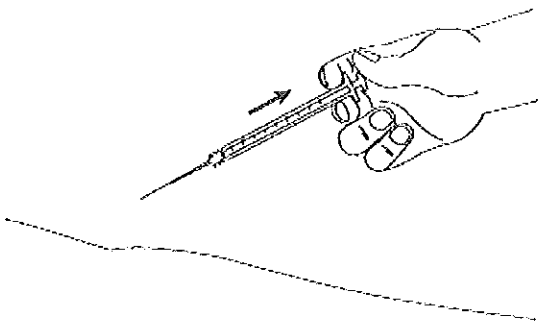
Step 6: Gently pinch the skin at the injection site and, holding the needle at an angle of approximately 45 degrees (as shown in the picture) insert it into the injection site.

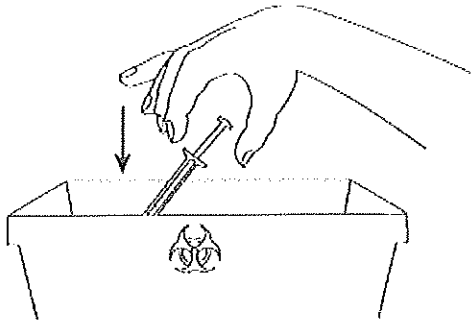
Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and insert it into a different injection site.



Step 7: Always keeping your skin pinched, slowly press down the plunger as far as it will go <u>until all the solution is injected</u>. Keep the plunger pressed down and hold the syringe in place for 5 seconds.

Step 8: Slowly release the skin fold and gently pull the needle out. Put the cover back on the needle.





Step 9: Dispose of the used syringe 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.

For Novartis Pharma AG, Basel, Switzerland

Further information is available from:

Novartis Healthcare Private Limited

Sandoz House, Dr. Annie Besant Road,

Worli, Mumbai 400 018, India.

Information issued: India package insert dtd 16 Apr 12 based on the International Package Leaflet (IPL) dtd 24 Feb 12.

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