SIGNIFOR®

Pasireotide diaspartate

NAME OF MEDICINE

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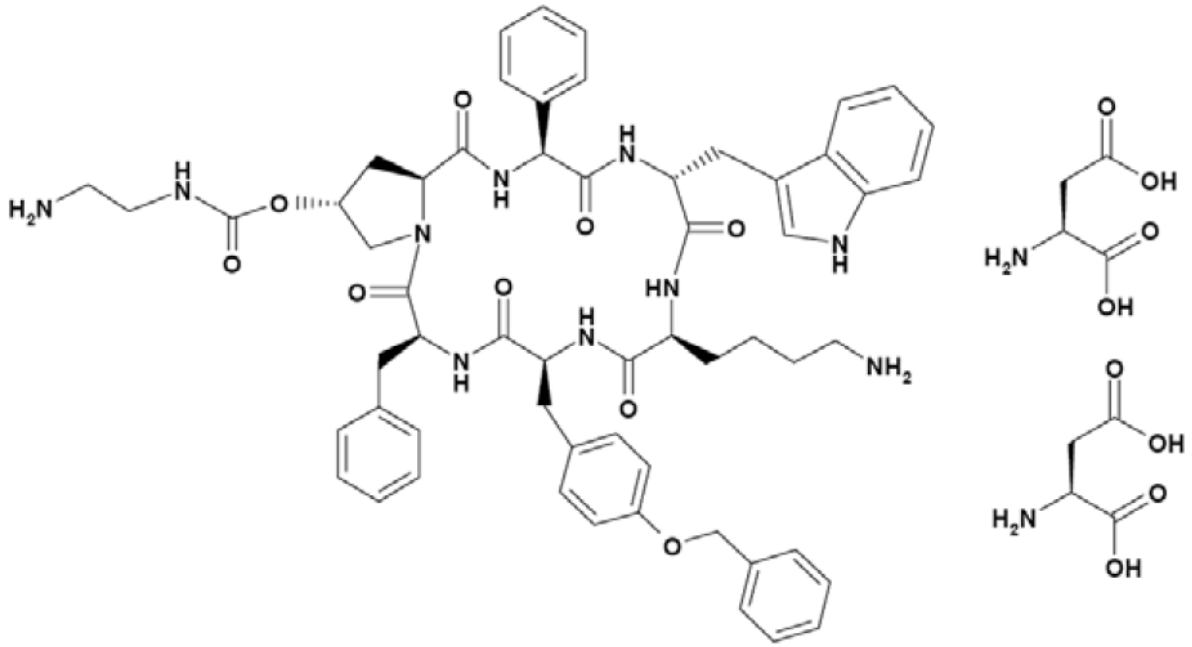


Pasireotide diaspartate CAS No.: 396091-77-3

Pasireotide CAS No.: 396091-73-9

Molecular weight: 1313.41 (for the diaspartate salt)

Pasireotide diaspartate is a white to slightly greyish powder. The drug substance is freely soluble in water and pKa has been determined at 10.2 and 9.1.

DESCRIPTION

Pasireotide 300 micrograms/1 mL, 600 micrograms/1 mL and 900 micrograms/1 mL solution for injection is clear and colourless. The free base is pasireotide and salt form is pasireotide diaspartate. The excipients are mannitol, tartaric acid, sodium hydroxide and water for injections. The formulations are isotonic and the pH is 4.2.

PHARMACOLOGY

Mechanism of Action

Pasireotide is a 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 1). Pasireotide binds with high affinity to four of the five hssts.

Table 1 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	> 100	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

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumours 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 tumour 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 1), 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 2 hours post dose. In one of the studies investigating a 1950 ug 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 1950 ug 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 b.i.d. (-10.39 bpm) and at 0.5 hours for pasireotide 1950 µg b.i.d. (-14.91 bpm). No episodes of torsade de pointes (transient or sustained) were observed.

Pharmacokinetics

In healthy volunteers, pasireotide demonstrates approximately linear pharmacokinetics (PK) for a wide dose range from 2.5 µg to 1500 µg. In Cushing's disease patients, pasireotide demonstrates linear dose-exposure relationship in a dose range from 300 µg to 1200 µg.

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. 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 faeces.

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 faeces and 7.63 ± 2.03% in urine.

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

Steady-state pharmacokinetics:

Following multiple s.c. doses, pasireotide demonstrates linear and time-independent pharmacokinetics in the dose range of 50 µg to 600 µg once a day (q.d.) in healthy volunteers, and 300 µg to 1200 µg 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 50, 200 and 600 µg q.d. doses).

Special populations:

<u>Elderly patients in the target population:</u>

Age has been found to be a covariate contributing to increased exposure 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.

<u>Paediatric patients:</u>

No studies have been performed in paediatric 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 TRIALS

A Phase III, multicenter, randomized study was conducted to evaluate the safety and efficacy of two dose levels of Signifor over a 6-month treatment period in Cushing's disease patients with persistent or recurrent disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery.

Patients with a baseline 24-hour urine free cortisol (UFC) >1.5 x upper limit of normal (ULN) were randomized to receive a Signifor dosage of either 600 mcg subcutaneous b.i.d. or 900 mcg subcutaneous b.i.d. After three months of treatment, patients with a mean 24-hour UFC $\leq$ 2.0 x ULN 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 300 mcg b.i.d. After the initial six months in the study, patients entered an additional 6-month open-label treatment period. The dosage could be reduced by 300 mcg b.i.d. at any time during the study for intolerability.

A total of 162 patients were enrolled in this study. The majority of patients were female (78%) and had persistent or recurrent Cushing's disease despite pituitary surgery (83%) with a mean age of 40 years. A few patients (4%) in either treatment group received previous pituitary irradiation. The median value of the baseline 24-hour UFC for all patients was 565 nmol/24 hours (normal range 30 to 145 nmol/24 hours). About two-thirds of all randomized patients completed six months of treatment.

The primary efficacy endpoint was the proportion of patients who achieved normalization of mean 24-hour UFC levels after six months of treatment and did not dose increase during this period.

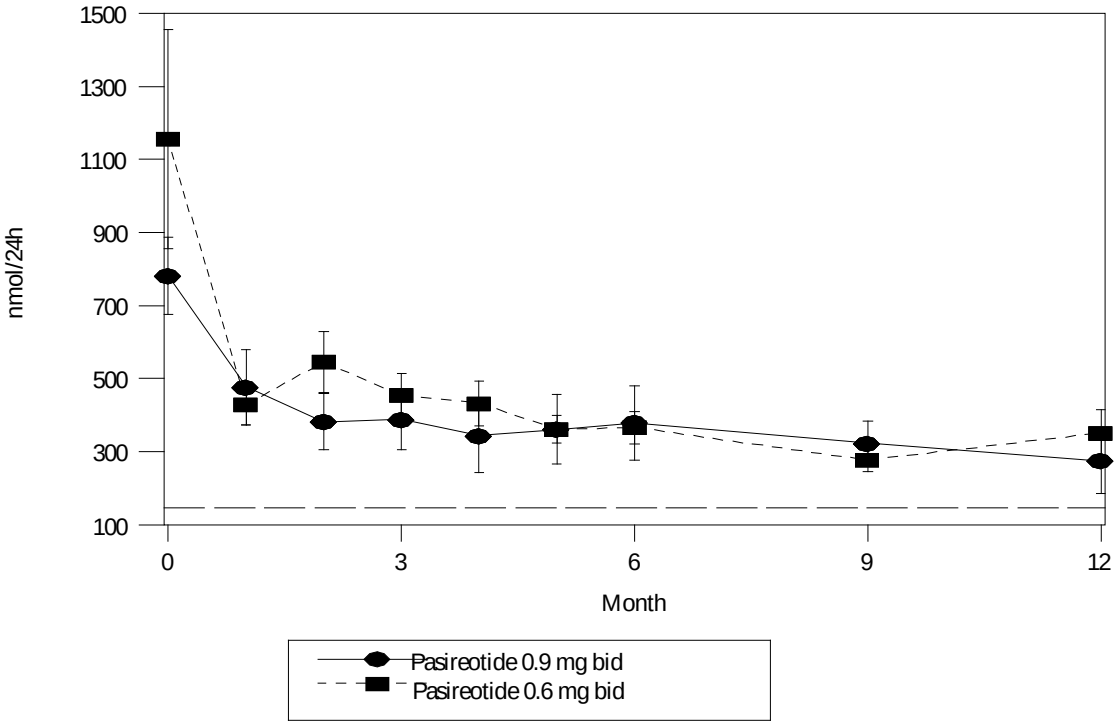
At Month 6, the percentages of responders for the primary endpoint were 15% and 26% in the 600 mcg b.i.d. and 900 mcg b.i.d. groups, respectively (Table 2). The percentages of patients with mUFC ≤ ULN or ≥ 50% reduction from baseline, a less stringent endpoint than the primary endpoint, were 34% in the 600 mcg bid and 41% in the 900 mcg bid groups. Dose increases appeared to have minimal effect on 24-hour UFC response. Mean and median percentage changes in UFC from baseline are presented in Table 2.

Table 2 24-Hour Urinary Free Cortisol (UFC) Study Results at Month 6 in Patients with Cushing's Disease

	SIGNIFOR 600 mcg b.i.d. N=82	SIGNIFOR 900 mcg b.i.d. N=80
UFC Responders		
n/N	12/82	21/80
% (95% CI)	15% (7%, 22%)	26% (17%, 36%)
UFC Levels (nmol/24hr)	N=78	N=72
Baseline		
Mean (SD)	868 (764)	750 (930)
Median	704	470
% Change from baseline		
Mean (95% CI)	-22% (-44%, +1%)	-42% (-50%, -33%)
Median	-47%	-46%

Signifor resulted in a decrease in the mean 24-hour UFC after 1 month of treatment (Figure 1). For patients (n=78) who stayed in the trial, similar UFC lowering was observed at Month 12.

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 24 hour UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12. At least two 24 hour 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.

Decreases from baseline for blood pressure were observed at Month 6, including patients who did not receive any antihypertensive medication. However, due to the fact that the study allowed initiation of antihypertensive medication and dose increases in patients already receiving such medications, the individual contribution of Signifor or of antihypertensive medication adjustments cannot be clearly established.

Facial rubor improved in 36.7% (18/49) and 59.6% (28/47) of patients treated with 600 and 900 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.

Individual patients showed varying degrees of improvement in Cushing's disease manifestations but because of the variability in response and the absence of a control group in this trial, it is uncertain whether these changes could be ascribed to the effects of Signifor.

INDICATIONS

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

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh C).

PRECAUTIONS

Effects on Fertility

It is unknown whether pasireotide has an effect on human fertility. Studies in rats have shown effects on female reproductive parameters.

Pasireotide did not affect fertility in male rats at subcutaneous doses up to 10 mg/kg/day (a dose 51-fold higher than the maximum recommended human dose (MRHD) based on surface area, mg/m^2). In female rats, fertility was decreased at daily doses of 0.1 mg/kg/day (0.5-fold the MRHD based on surface area, mg/m^2) as shown by decreased numbers of implantation sites and viable fetuses. Decreased corpora lutea and abnormal cycles or acyclicity were observed at 1 mg/kg/day (5-fold higher than the MRHD based on surface area, mg/m^2). This effect is consistent with the pharmacological action of pasireotide to inhibit IGF-1 secretion.

Use in Pregnancy – Category B3

There are no adequate and well-controlled studies in pregnant women and women of child bearing age. Studies in animals have shown evidence of an increased occurrence of fetal damage. The potential risk for humans is not known.

In embryofetal development studies in rats and rabbits, no direct teratogenic effect of pasireotide was observed at maternally toxic doses (respectively 10 and 5 mg/kg/day by subcutaneous injection) leading to exposures (plasma AUC 0 to 24 hrs) respectively 145- and 40-fold higher than in patients at the MRHD. At 10 mg/kg/day in rats, the frequency of early/total resorptions and malrotated limbs was increased, fetal weight was decreased and

ossification was impaired. 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 also seen in rabbits at 1 mg/kg/day (6.5-fold the plasma AUC at the MRHD).

Labour and delivery:

No data in humans are available.

Pasireotide had no effects on labour and delivery in rats administered up to 10 mg/kg/day (52-fold higher than the MRHD based on surface area, mg/m^2).

Signifor should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Use in Lactation

It is not known whether pasireotide is excreted in human milk. Available data in rats have shown excretion of pasireotide in milk. As a risk to the breastfed child cannot be excluded, Signifor should not be used by the nursing mother.

Retardation of physiological growth, attributed to GH inhibition was observed at all doses tested (≥2 mg/kg/day by subcutaneous injection; ≥10-fold higher than the MRHD based on surface area, mg/m^2) in 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.

Paediatric Use

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

Use in the Elderly

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 Pharmacology)

Hypocortisolism

Treatment with Signifor leads to a rapid suppression of ACTH (adrenocorticotropic hormone) secretion in Cushing's disease patients. Suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially hypocortisolism. Cases of hypocortisolism have been reported in the Phase III study in Cushing's disease patients (see Adverse effects),

generally within the first two months of treatment. 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.

Hyperglycaemia/hypoglycaemia and Diabetes

Elevations in blood glucose levels have been seen in healthy volunteers and patients treated with Signifor. In the Phase 3 trial, nearly all patients (including those with normal glucose status at baseline, pre-diabetes, and diabetes) developed worsening glycaemia in the first two weeks of treatment. Cushing's disease patients with poor glycaemic control (as defined by HbA1c values >8% while receiving anti-diabetic therapy) may be at a higher risk of developing severe hyperglycaemia and associated complications, e.g. ketoacidosis. Because of this predictable adverse reaction, the glycaemic status must be assessed prior to starting treatment with Signifor and regularly monitored.

Hypoglycaemia was also observed in subjects participating in clinical trials with pasireotide (see Adverse effects) but less frequently than hyperglycaemia.

In patients with uncontrolled diabetes mellitus intensive anti-diabetic therapy should be initiated prior to treatment with Signifor. During treatment, additional monitoring and dose adjustments of the anti-diabetic therapy (including insulin) may be necessary.

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, glycaemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

If hyperglycaemia 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. The optimal treatment for the management of Signifor-induced hyperglycaemia is not known. If uncontrolled hyperglycaemia persists despite appropriate medical management the dose of Signifor should be reduced or the treatment discontinued.

In patients with poor glycaemic 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 Adverse effects). 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 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 Adverse effects). 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. 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 Adverse effects). 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.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies by the subcutaneous route were (2 years duration) conducted in rats and transgenic mice (6 months). No carcinogenic activity was observed with pasireotide in transgenic mice, involving administration of doses up to 2.5 mg/kg/day (yielding plasma AUC values 10–13 times higher than in patients at the maximum recommended human dose [MRHD]. Injection site tumours (fibromas) were increased in incidence in male rats at a dose of 0.3 mg/kg/day (>16 times the maximum recommended human dose on a mg/kg basis). This finding is consistent with a response to continuous irritation/inflammation at the repeatedly injected site and is not considered to indicate a carcinogenic potential in humans. No treatment-related increase in systemic tumours in male rats or tumours in female rats was seen up to the highest dose tested (0.3 mg/kg/day; yielding 14 times [males] and 7 times [females] the plasma AUC in patients at the MRHD.

INTERACTIONS WITH OTHER MEDICINES

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 inducer of P-gp. In addition, at therapeutic dose levels, pasireotide is not expected to be:

- a substrate, inhibitor or inducer 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 P-gp, BCRP, 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*.

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 cannot be excluded based on available data. Caution should be exercised 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 cyclosporin by reducing its intestinal absorption. It is unknown whether such interaction occurs in humans. Therefore dose adjustments of cyclosporin may be required when co-administering pasireotide and cyclosporin (see Precautions).

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

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.

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 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), anticholinergics (e.g. ipratropium bromide, oxybutynin), certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil), certain antiarrhythmics (see also section Precautions).

Insulin and anti-diabetic 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 Precautions).

ADVERSE EFFECTS

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 hyperglycaemia.

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 600 mcg or 900 mcg 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 diarrhoea, nausea, abdominal pain, cholelithiasis, hyperglycemia, diabetes mellitus, fatigue and glycosylated haemoglobin increased. There were no deaths during the study.

Adverse events reported up to the cut-off date of the analysis, with an overall frequency higher than 5% are presented in Table 3 by randomized dose group and overall. Adverse events are ranked by frequency, with the most frequent reactions listed first.

Table 3 Adverse events [n(%)] with an overall frequency of more than 5% in the combined dose group in the Phase III study in Cushing's Disease patients

	SIGNIFOR 600 mcg bid N=82	SIGNIFOR 900 mcg bid N=80	Overall N=162
Diarrhea	48 (59)	46 (58)	94 (58)
Nausea	38 (46)	46 (58)	84 (52)
Hyperglycaemia	31 (38)	34 (43)	65 (40)
Cholelithiasis	25 (30)	24 (30)	49 (30)
Headache	23 (28)	23 (29)	46 (28)
Abdominal pain	19 (23)	20 (25)	39 (24)
Fatigue	12 (15)	19(24)	31 (19)
Diabetes mellitus	13 (16)	16 (20)	29 (18)
Injection site reactions	14 (17)	14 (18)	28 (17)
Nasopharyngitis	10 (12)	11 (14)	21 (13)
Alopecia	10 (12)	10 (13)	20 (12)
Asthenia	13 (16)	5 (6)	18 (11)
Glycosylated hemoglobin increased	10 (12)	8 (10)	18 (11)
Alanine aminotransferase increased	11 (13)	6 (8)	17 (10)
Gamma-glutamyl transferase increased	10 (12)	7 (9)	17 (10)

Edema peripheral	9 (11)	8 (10)	17 (10)
Abdominal pain upper	10 (12)	6 (8)	16 (10)
Decreased appetite	7 (9)	9 (11)	16 (10)
Hypercholesterolemia	7 (9)	9 (11)	16 (10)
Hypertension	8 (10)	8 (10)	16 (10)
Dizziness	8 (10)	7 (9)	15 (9)
Hypoglycaemia	12 (15)	3 (4)	15 (9)
Type 2 diabetes mellitus	10 (12)	5 (6)	15 (9)
Anxiety	5 (6)	9 (11)	14 (9)
Influenza	9 (11)	5 (6)	14 (9)
Insomnia	3 (4)	11 (14)	14 (9)
Myalgia	10 (12)	4 (5)	14 (9)
Arthralgia	5 (6)	8 (10)	13 (8)
Pruritus	6 (7)	7 (9)	13 (8)
Lipase increased	7 (9)	5 (6)	12 (7)
Constipation	7 (9)	4 (5)	11 (7)
Hypotension	5 (6)	6 (8)	11 (7)
Vomiting	3 (4)	8 (10)	11 (7)
Back pain	4 (5)	6 (8)	10 (6)
Dry skin	5 (6)	5 (6)	10 (6)
Electrocardiogram QT prolonged	5 (6)	5 (6)	10 (6)
Hypokalemia	6 (7)	4 (5)	10 (6)
Pain in extremity	6 (7)	4 (5)	10 (6)
Sinus bradycardia	8 (10)	2 (3)	10 (6)
Vertigo	4 (5)	6 (8)	10 (6)
Abdominal distension	4 (5)	5 (6)	9 (6)
Adrenal insufficiency	4 (5)	5 (6)	9 (6)
Aspartate aminotransferase increased	6 (7)	3 (4)	9 (6)
Blood glucose increased	6 (7)	3 (4)	9 (6)

Other notable adverse events which occurred with a frequency less than 5% were: anemia (4%); blood amylase increased (2%) and prothrombin time prolonged (2%).

Description of Selected Adverse Drug Reactions

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 glycaemia at study entry in comparison to pre-diabetic patients or diabetic patients (Table 4).

Table 4 Changes in mean HbA1c at month 6 according to glycaemic status at study entry

Glycemic status at study entry (n = overall number of patients)	600 mcg b.i.d.		900 mcg b.i.d.	
	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 hyperglycaemia 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 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, haemorrhage 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 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 cholelithiasis and acute pancreatitis.

DOSAGE AND ADMINISTRATION

Dose

The recommended dosage range of SIGNIFOR is 300 mcg to 900 mcg by subcutaneous injection, twice a day. The recommended initial dose is 600 mcg or 900 mcg twice a day. Titrate dose based on response and tolerability.

For patients who are started on 600 mcg twice a day, a dosage increase to 900 mcg twice a day may be considered based on the response to the treatment as long as the 600 mcg dosage is well tolerated by the patient. Individualized dose reduction may be considered for patients with a stable response at the discretion of the treating physician.

Patients should be evaluated for treatment response (clinically meaningful reduction in Urinary Free Cortisol (UFC) levels and/or improvement in signs or symptoms of the disease) and should continue receiving therapy with Signifor as long as benefit is derived. Maximum urinary free cortisol reduction is typically seen by two months of treatment. Patients who do not experience clinical benefit from Signifor should be considered for discontinuation.

Management of suspected adverse reactions may require temporary dose reduction of Signifor. Dose reduction by decrements of 300 mcg twice a day is suggested.

Dose adjustment in:

Renal insufficiency:

No dosage adjustment is required in patients with impaired renal function (see Pharmacology).

Hepatic insufficiency:

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 300 mcg twice a day (see Pharmacology). The maximum recommended dose for patients with moderate hepatic impairment is 600 mcg twice a day only following careful consideration of the perceived risks and benefits to the individual, and with frequent clinical review and monitoring of liver function. Signifor should not be used in patients with severe hepatic impairment (Child Pugh C) (see Contraindications and Precautions).

Diabetes:

For patients with pre-diabetes or diabetes mellitus an initial dose of 600 mcg twice a day may be considered (see Precautions).

Paediatric patients:

Signifor is not recommended for use in paediatric 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 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).

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.

Product is for single use in one patient only. Discard any residue.

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 diarrhoea 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Dosage Form

Injection, solution

Quantity of active ingredient:

Each ampoule of 1 mL contains:

- 300 microgram pasireotide (as diaspartate)
- 600 microgram pasireotide (as diaspartate)
- 900 microgram pasireotide (as diaspartate)

Container type:

Colourless glass ampoule.

Pack sizes 300 micrograms/ 1mL, 600 micrograms/ 1mL and 900 micrograms/ 1mL:

Packs containing *6 ampoules or multipacks containing *30 x (5 packs of 6) or 60 x (10 packs of 6) ampoules. *Not all pack sizes may be marketed.

Appearance:

Pasireotide solution for injection is a clear, colourless solution in a 1 mL one point cut colourless glass ampoule.

Storage Conditions

Store below 25 °C. Store in original package (in order to protect it from light). Signifor must be kept out of the reach and sight of children.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd

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North Ryde 2113

Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

01 November 2013

DATE OF MOST RECENT AMENDMENT

Not applicable.

Signifor is a registered trademark.

For internal use only: (som011113i) based on CDS 31-Jan-13