PRODUCT MONOGRAPH

Pr SIGNIFOR®

(Pasireotide Injection)

0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL
pasireotide (as pasireotide diaspartate)

SYNTHETIC PASIREOTIDE ANALOGUE OF SOMATOSTATIN

Recordati Rare Diseases Canada Inc.
Toronto, Ontario, Canada M4N 3N1

Date of Preparation:
September 23, 2013

Control No: 234503

Date of Revision:
July 8, 2020

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Pr SIGNIFOR®

(Pasireotide Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
subcutaneous (s.c.)	Each ampoule 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).	Mannitol, sodium hydroxide, tartaric acid, water for injections *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING**

INDICATIONS AND CLINICAL USE

SIGNIFOR (pasireotide) is indicated for:

- Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit or normalization of urinary free cortisol (UFC) (or >50% decrease in UFC) are derived.

SIGNIFOR should be prescribed and supervised by a qualified physician. To receive SIGNIFOR, patient must be enrolled in the Access Program for SIGNIFOR.

Geriatrics (≥ 65 years of age):
Data on Cushing's disease patients older than 65 years are too limited to determine whether they respond differently from younger subjects.

Pediatrics (< 18 years of age):
SIGNIFOR should not be used in pediatric patients. There are no clinical data available in patients under 18 years of age.

CONTRAINDICATIONS

SIGNIFOR (pasireotide) is contraindicated in:

- Patients with moderate or severe hepatic impairment (Child-Pugh B or C).
- Patients with uncontrolled diabetes (≥8% HbA1c), despite receiving anti-diabetic

therapy.

- Patients with the following cardiovascular conditions:
  - NYHA Class III to IV heart failure
  - Cardiogenic shock
  - Second or third degree atrioventricular (AV) block, sinoatrial block, or sick sinus syndrome (unless patient has a functioning pacemaker)
  - Severe bradycardia
  - Congenital long QT syndrome or baseline QTc interval ≥500 ms
- Patients who are hypersensitive to pasireotide or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

RISK OF HEPATOTOXICITY:

- Elevations in liver aminotransferases are commonly observed with pasireotide (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**; **ADVERSE REACTIONS**).
- 4 cases (3 healthy volunteers and 1 Cushing's disease patient) that met the biochemical criteria for Hy's Law have been reported in Clinical Trials (see **WARNINGS AND PRECAUTIONS**; **ADVERSE REACTIONS**).

RISK OF CARDIOVASCULAR (CV) ADVERSE EVENTS (AEs):

- Pasireotide can cause bradycardia and atrioventricular block (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS**; **ADVERSE REACTIONS**; **ACTION AND CLINICAL PHARMACOLOGY**).
- Pasireotide has been shown to prolong the QTc interval on the ECG (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS**; **ACTION AND CLINICAL PHARMACOLOGY**).

RISK OF HYPERGLYCEMIA:

- Frequent, significant alterations in blood glucose levels have been seen in healthy volunteers and Cushing's disease patients treated with pasireotide (see **ADVERSE REACTIONS**; **CLINICAL TRIALS**).

Cardiovascular

Bradycardia and PR Interval Prolongation: Pasireotide causes a decrease in heart rate and PR interval prolongation (see **ACTION AND CLINICAL PHARMACOLOGY - Cardiac Electrophysiology**). Careful monitoring of patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, ischemic heart disease, or congestive heart failure is recommended. Concomitant medications that decrease heart rate, prolong the PR interval and/or prolong the QTc interval should be avoided to the extent possible during

treatment with SIGNIFOR (see **DRUG INTERACTIONS**).

QTc Prolongation: Pasireotide is associated with QTc prolongation (see **ADVERSE REACTIONS**; **ACTION AND CLINICAL PHARMACOLOGY - Cardiac Electrophysiology**). SIGNIFOR should not be used in patients with congenital long QT syndrome (see **CONTRAINDICATIONS**). SIGNIFOR should be used with caution in patients who are at significant risk of developing prolongation of QT, including, but not limited to, the following:

- QTc prolongation at baseline or a family history of sudden cardiac death at <50 years
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, unstable angina or clinically significant bradycardia, a history of significant arrhythmias, or any other risk factors for torsades de pointes
- taking other substances that are known to lead to QT prolongation, including anti-arrhythmic medicinal products (see **DRUG INTERACTIONS**).
- diabetes mellitus, especially with autonomic neuropathy
- with hypokalemia, hypocalcaemia and/or hypomagnesaemia (see **WARNINGS AND PRECAUTIONS - Renal**)

Female gender and age 65 years or older are risk factors for torsade de pointes.
Monitoring for an effect on the QTc interval is advisable. A baseline ECG is recommended prior to initiating therapy with SIGNIFOR and as clinically indicated.

Concomitant medications that cause QTc prolongation should be avoided during treatment with SIGNIFOR (see **DRUG INTERACTIONS**).When drugs that prolong the QTc interval are prescribed, healthcare professionals should consider the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug in consultation with the patient.

Endocrine and Metabolism

Hypocortisolism
Treatment with SIGNIFOR leads to a rapid suppression of adrenocorticotropic hormone (ACTH) secretion in Cushing's disease patients which 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 **ADVERSE 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, hyponatraemia or hypoglycaemia). 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
In the pivotal trial, a mean increase in HbA1c of approximately 1.5% relative to baseline occurred early during treatment and continued throughout the duration of the trial. Of patients with normal (≤6%) HbA1c at baseline, 62% became either pre-diabetic or diabetic by month 6. The effect of SIGNIFOR on hyperglycemia was both dose-dependent and higher in patients with pre-diabetic conditions or established, controlled diabetes mellitus at baseline. During the trial, the use of antihyperglycemic agents increased from 6.2% to 22.8% for insulin, from 0.6% to 9.3% for glinides, from 1.9% to 21.6% for sulphonamides, and from 15.4% to 43% for metformin. Patients with uncontrolled diabetes (≥8% HbA1c) were excluded from the trial (see **CONTRAINDICATIONS**).

Once SIGNIFOR treatment has been initiated, monitoring of blood glucose should be done weekly for the first two to three months and at least once monthly after a stable dose of SIGNIFOR has been established. Weekly monitoring should be resumed for two to three months after a dose increase (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**). If uncontrolled hyperglycemia persists, despite appropriate medical management, the dose of SIGNIFOR should be reduced or discontinued.

There have been post-marketing cases of ketoacidosis in patients taking SIGNIFOR including in patients without a history of diabetes or without other underlying risk factors. In some cases, factors predisposing to ketoacidosis such as acute illness, infection, pancreatic disorders (e.g. pancreatic malignancy or pancreatic surgery), and alcohol abuse were present. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of diabetes history, and SIGNIFOR treatment should be stopped with close monitoring of the patient.

SIGNIFOR should not be administered to Cushing's disease patients with poor glycemic control (as defined by HbA1c values ≥8% while receiving anti-diabetic therapy) as they may be at a higher risk of developing severe hyperglycemia and associated complications (e.g. ketoacidosis) (see **CONTRAINDICATIONS**).

Pituitary hormones
Cushing's disease patients with persistent or recurrent disease might 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.

Hematologic
The safety of the combination of SIGNIFOR with anticoagulants has not been established. Patients should be monitored regularly for alterations in their coagulation parameters and the anticoagulant dose should be adjusted accordingly (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Hepatic/Biliary/Pancreatic

Hepatic

In the pivotal trial, the proportions of patients with shifts in hepatobiliary biochemistry parameters from normal to high were: 30.8% for GGT, 24.4% for AST, 32.1% for ALT and 3.2% for total bilirubin. Eight Cushing's patients (5.1%) had elevations of ALT or AST > 3x upper limit of normal (ULN). Concurrent elevations of ALT or AST >3x ULN and total bilirubin ≥2xULN, meeting the definition of Hy's Law, were reported within 4-10 days of initiating treatment with SIGNIFOR in 3 healthy volunteers and one Cushing's patient (see **ADVERSE REACTIONS**). The cases had an early onset and the patient with Cushing's disease developed jaundice. Liver test elevations resolved upon discontinuation of SIGNIFOR.

Monitoring of liver function is recommended prior to treatment with pasireotide, weekly for one month, every two weeks for 3 months and every 3 months on treatment thereafter. Close monitoring should be resumed with any dose increase (see **WARNINGS AND PRECAUTIONS –** Monitoring and Laboratory Tests).

Patients who develop increased transaminase levels should be monitored closely.

If elevations of ALT are above 5 times the ULN or if ALT or AST elevations greater than 3 x ULN occur concurrently with bilirubin elevations greater than 2 x ULN, or if the patient develops jaundice or other signs suggestive of clinically significant liver impairment, discontinue SIGNIFOR treatment and investigate for probable cause of the findings. If elevations of ALT exceed 3 times the ULN but are below 5 times the ULN, repeat the test within 48 hours. If the values are confirmed below 5 times the upper limit of normal, keep on monitoring every 48 hours. If the values rise above five times the ULN, discontinue SIGNIFOR treatment. Following discontinuation of treatment with pasireotide, patients should be monitored until resolution. Treatment should not be restarted. Concomitant medications with hepatotoxic potential should be used with caution during treatment with SIGNIFOR.

Pancreatic

Elevations in lipase and amylase were observed in patients receiving pasireotide in clinical studies. Twenty-one (13%) patients reported pancreatitis-related adverse events. The elevations were reversible while continuing treatment (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**). Elevations in lipase and amylase were more pronounced in patients with renal impairment (see **WARNINGS AND PRECAUTIONS – Renal**).

Biliary

Cholelithiasis (gallstones) has been frequently reported in clinical studies with pasireotide (see **ADVERSE REACTIONS**). There have been post-marketing cases of cholelithiasis in patients taking SIGNIFOR, resulting in serious complications including cholecystitis and cholangitis, which have sometimes required cholecystectomy.

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; stones should be managed according to clinical practice. If

complications of cholelithiasis are suspected, discontinue SIGNIFOR and treat appropriately.

Renal
Hypokalemia, hypocalcaemia or hypomagnesaemia must be corrected prior to SIGNIFOR administration and electrolytes should be monitored periodically during therapy (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**). Caution should be observed in patients in conditions that can lead to electrolyte imbalances (e.g., diarrhea, use of diuretics).

The use of SIGNIFOR with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

In a clinical study of single dose pasireotide s.c, 900 µg, grade 3 and grade 4 increases in amylase, lipase and uric acid and grade 3 decreases in hemoglobin were observed in subjects with severe renal impairment and ESRD. SIGNIFOR should be used with caution in patients with severe renal impairment and ESRD (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**, **DOSAGE AND ADMINISTRATION**, **ACTION AND CLINICAL PHARMACOLOGY**).

Sexual Function/Reproduction
A reduction or normalization of serum cortisol levels in female patients with Cushing's disease treated with SIGNIFOR could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception during treatment with SIGNIFOR (see **WARNINGS AND PRECAUTIONS – Special Populations**). Studies in rats with pasireotide via the s.c. route have shown effects on female reproductive parameters (see **TOXICOLOGY**). The clinical relevance of these effects in humans is unknown.

Special Populations

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 should be instructed to use effective contraception during treatment with SIGNIFOR, and also advised that treatment with SIGNIFOR could potentially restore fertility.

Pregnant Women: SIGNIFOR should not be used during pregnancy. There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is not known (see **TOXICOLOGY**).

Nursing Women: SIGNIFOR should not be used in nursing women. 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 **DETAILED PHARMACOLOGY, Nonclinical Pharmacokinetics**). A risk to the breastfed child cannot be excluded.

Pediatrics (< 18 years of age): SIGNIFOR should not be used in pediatric patients. There are no clinical data available in patients under 18 years of age.

Geriatrics (≥ 65 years of age): There are limited data on the use of SIGNIFOR in patient 65 years and older. Clinical studies of SIGNIFOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment: No dose adjustment is required in patients with impaired renal function. SIGNIFOR should be used with caution in patients with severe renal impairment and ESRD (see **WARNINGS AND PRECAUTIONS – Renal**, **WARNINGS AND PRECAUTIONS-Monitoring and laboratory tests**, **DOSAGE AND ADMINISTRATION**, **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment: SIGNIFOR is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

Monitoring and Laboratory Tests

Patients should be evaluated for treatment response (Normalization or >50% decrease 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 therapy with SIGNIFOR should be considered for discontinuation as studies have shown that non-responders do not usually improve after this time period.

Hypocortisolism: It is necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia or hypoglycaemia).

Liver Chemistry: Monitoring of liver chemistry is recommended prior to treatment with SIGNIFOR (see **CONTRAINDICATIONS**). Upon treatment initiation, liver chemistry should be monitored weekly for one month, every two weeks for 3 months and every 3 months thereafter. Four cases meeting the biochemical criteria for Hy's law have been reported within 4-10 days of initiating treatment with SIGNIFOR. Close monitoring of liver function should be resumed with any dose increase (see **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic**).

Electrocardiograms: A baseline ECG is recommended prior to initiating therapy with SIGNIFOR (see **CONTRAINDICATIONS**), followed by periodic ECG monitoring during treatment, as clinically indicated, for effects on the QTc interval, heart rate and AV conduction (see **WARNINGS AND PRECAUTIONS - Cardiovascular**).

Electrolytes: Hypokalemia, hypocalcaemia or hypomagnesaemia must be corrected prior to SIGNIFOR administration and electrolytes should be monitored periodically during therapy.

Glycemic Status: Glycemic status (fasting plasma glucose/hemoglobin A1c [FPG/HbA1c]) should be assessed prior to starting treatment with pasireotide. Monitoring of blood glucose

should be done weekly for the first two to three months and at least once monthly after a stable dose of SIGNIFOR has been established. Weekly monitoring of blood glucose should be resumed for two to three months after a dose increase (see **WARNINGS AND PRECAUTIONS – Endocrine and Metabolism, Glucose Metabolism**).

Lipase: Lipase should be monitored prior to onset of therapy with SIGNIFOR and periodically during treatment, especially in patients with severe renal impairment and ESRD.

Gallbladder Ultrasound: Ultrasonic examination of the gallbladder before, and at 6- to 12-month intervals during SIGNIFOR therapy is recommended (see **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic, Gallbladder and related events**).

Pituitary Function: 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.

Cyclosporine: Cyclosporine level should be monitored to maintain therapeutic levels (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Hematologic: Monitoring of coagulation parameters should be performed in patients treated concomitantly with SIGNIFOR and anticoagulant drugs (see **WARNINGS AND PRECAUTIONS – Hematologic** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 201 Cushing's disease patients received SIGNIFOR in Phase II (N=39) and Phase III (N=162) studies.

In the pivotal study, adverse drug reactions (ADRs) that led to study discontinuation were reported in 28 (17.3%) patients. The most common were hyperglycemia-related [10 (6%)], gamma-glutamyltransferase increase [5 (3.1%)], diabetes mellitus [4 (2.5%)] and diarrhea [3 (1.9%)]. The most common adverse drug reactions requiring clinical intervention (dose adjustment/interruption or requiring additional therapy) were metabolism/nutrition adverse reactions related to hyperglycemia, GI-related (abdominal pain, diarrhea, nausea), adrenal insufficiency and cholelithiasis.

The most common ADRs (incidence ≥10%) were diarrhea, nausea, abdominal pain, cholelithiasis, hyperglycemia, diabetes mellitus, fatigue and glycosylated hemoglobin increase. Serious ADRs were reported in 11.7% of patients. Serious ADRs (≥ 1% incidence in all patients) included cholelithiasis, diabetes mellitus and hyperglycemia which were reported in 4 (2.5%) patients, each, and adrenal insufficiency reported in 2 (1.2%) patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction

rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reactions reported, with an overall frequency higher than or equal to 1% are presented in Table 1 by randomised dose group.

Table 1 - Adverse drug reactions with an overall frequency of greater than or equal to 1% in the Phase III study in Cushing's disease patients

Primary system organ class Preferred term	Pasireotide 600 ug bid N=82 n (%)	Pasireotide 900 ug bid N=80 n (%)	Overall N=162 n (%)
Cardiac disorders			
Sinus bradycardia	6(7.3)	1(1.3)	7(4.3)
Ear and labyrinth disorders			
Vertigo	1(1.2)	3(3.8)	4(2.5)
Endocrine disorders			
Adrenal insufficiency	4(4.9)	5(6.3)	9(5.6)
Eye disorders			
Vision blurred	0(0.0)	2(2.5)	2(1.2)
Gastrointestinal disorders			
Diarrhea	46(56.1)	43(53.8)	89(54.9)
Nausea	33(40.2)	43(53.8)	76(46.9)
Abdominal pain	14(17.1)	19(23.8)	33(20.4)
Vomiting	2(2.4)	8(10.0)	10(6.2)
Abdominal pain upper	6(7.3)	3(3.8)	9(5.6)
Flatulence	4(4.9)	2(2.5)	6(3.7)
Abdominal distension	2(2.4)	3(3.8)	5(3.1)
Dry mouth	4(4.9)	1(1.3)	5(3.1)
Frequent bowel movements	3(3.7)	2(2.5)	5(3.1)
Abdominal discomfort	2(2.4)	1(1.3)	3(1.9)
Constipation	2(2.4)	1(1.3)	3(1.9)
Dyspepsia	0(0.0)	3(3.8)	3(1.9)
General disorders and administration site conditions			
Injection site reaction*	13(15.9)	13(16.3)	26(16.0)
Fatigue	7(8.5)	12(15.0)	19(11.7)

Primary system organ class Preferred term	Pasireotide 600 ug bid N=82 n (%)	Pasireotide 900 ug bid N=80 n (%)	Overall N=162 n (%)
Asthenia	6(7.3)	1(1.3)	7(4.3)
Malaise	2(2.4)	3(3.8)	5(3.1)
Microlithiasis	1(1.2)	1(1.3)	2(1.2)
Hepatobiliary disorders			
Cholelithiasis	25(30.5)	23(28.8)	48(29.6)
Cholecystitis	3(3.7)	1(1.3)	4(2.5)
Cholestasis	2(2.4)	2(2.5)	4(2.5)
Hepatic steatosis	1(1.2)	2(2.5)	3(1.9)
Biliary colic	0(0.0)	2(2.5)	2(1.2)
Injury, poisoning and procedural complications			
Procedural nausea	1(1.2)	2(2.5)	3(1.9)
Contusion	0(0.0)	2(2.5)	2(1.2)
Investigations			
Glycosylated haemoglobin increased	10(12.2)	7(8.8)	17(10.5)
Gamma-glutamyltransferase increased	8(9.8)	7(8.8)	15(9.3)
Alanine aminotransferase increased	9(11.0)	5(6.3)	14(8.6)
Lipase increased	7(8.5)	5(6.3)	12(7.4)
Blood glucose increased	6(7.3)	3(3.8)	9(5.6)
Aspartate aminotransferase increased	5(6.1)	3(3.8)	8(4.9)
Creatinine renal clearance decreased	3(3.7)	3(3.8)	6(3.7)
Electrocardiogram QT prolonged	3(3.7)	3(3.8)	6(3.7)
Weight decreased	1(1.2)	5(6.3)	6(3.7)
Blood insulin decreased	1(1.2)	4(5.0)	5(3.1)
Blood creatinine increased	2(2.4)	2(2.5)	4(2.5)
Blood amylase increased	4(4.9)	0(0.0)	4(2.5)
Blood urea increased	2(2.4)	1(1.3)	3(1.9)
Vitamin B12 decreased	2(2.4)	1(1.3)	3(1.9)
Activated partial thromboplastin time prolonged	1(1.2)	1(1.3)	2(1.2)
Blood alkaline phosphatase increased	2(2.4)	0(0.0)	2(1.2)
Blood cholesterol increased	1(1.2)	1(1.3)	2(1.2)
Cortisol free urine decreased	1(1.2)	1(1.3)	2(1.2)
Low density lipoprotein increased	2(2.4)	0(0.0)	2(1.2)
Prothrombin time prolonged	0(0.0)	2(2.5)	2(1.2)
Metabolism and nutrition disorders			
Hyperglycaemia	31(37.8)	32(40.0)	63(38.9)
Diabetes mellitus	13(15.9)	16(20.0)	29(17.9)
Type 2 diabetes mellitus	10(12.2)	5(6.3)	15(9.3)
Decreased appetite	6(7.3)	7(8.8)	13(8.0)
Hypoglycaemia	6(7.3)	0(0.0)	6(3.7)
Glucose tolerance impaired	2(2.4)	2(2.5)	4(2.5)
Hypercholesterolaemia	3(3.7)	0(0.0)	3(1.9)
Hyperlipidaemia	1(1.2)	1(1.3)	2(1.2)
Hypertriglyceridaemia	2(2.4)	0(0.0)	2(1.2)
Polydipsia	1(1.2)	1(1.3)	2(1.2)
Musculoskeletal and connective tissue disorders			
Myalgia	6(7.3)	1(1.3)	7(4.3)

Primary system organ class Preferred term	Pasireotide 600 ug bid N=82 n (%)	Pasireotide 900 ug bid N=80 n (%)	Overall N=162 n (%)
Arthralgia	3(3.7)	1(1.3)	4(2.5)
Muscular weakness	1(1.2)	1(1.3)	2(1.2)
Nervous system disorders			
Headache	5(6.1)	7(8.8)	12(7.4)
Dizziness	3(3.7)	3(3.8)	6(3.7)
Dysgeusia	3(3.7)	3(3.8)	6(3.7)
Somnolence	2(2.4)	2(2.5)	4(2.5)
Migraine	0(0.0)	2(2.5)	2(1.2)
Syncope	1(1.2)	1(1.3)	2(1.2)
Tremor	1(1.2)	1(1.3)	2(1.2)
Renal and urinary disorders			
Polyuria	1(1.2)	1(1.3)	2(1.2)
Skin and subcutaneous tissue disorders			
Alopecia	4(4.9)	5(6.3)	9(5.6)
Skin exfoliation	5(6.1)	3(3.8)	8(4.9)
Pruritus	4(4.9)	4(5.0)	8(4.9)
Dry skin	3(3.7)	2(2.5)	5(3.1)
Hyperhidrosis	1(1.2)	2(2.5)	3(1.9)
Rash	2(2.4)	0(0.0)	2(1.2)
Urticaria	0(0.0)	2(2.5)	2(1.2)
Ecchymosis	0(0.0)	2(2.5)	2(1.2)
Vascular disorders			
Hypotension	2(2.4)	4(5.0)	6(3.7)
Flushing	1(1.2)	2(2.5)	3(1.9)
Haematoma	1(1.2)	1(1.3)	2(1.2)
Hypertension	1(1.2)	1(1.3)	2(1.2)

*"Injection site reaction" encompasses the following preferred terms: injection site erythema, injection site hematoma, injection site hemorrhage, injection site irritation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, immediate post-injection reaction.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

ADRs which occurred with a frequency less than 1% (each ADR below represents 1 patient (0.6%) occurrence) were:

Blood and lymphatic disorders: Lymphocytosis, anemia

Cardiac disorders: Palpitations, sinus tachycardia, supraventricular tachycardia. A serious event of second degree atrioventricular block was reported in one subject (0.6%).

Endocrine disorders: Hypothyroidism, pituitary-dependent Cushing's syndrome

Gastrointestinal disorders: Gastroesophageal reflux disease, haemorrhoids, intestinal polyp, intra-abdominal haemorrhage, retching, salivary hypersecretion, stomatitis, tooth loss

General disorders and administration site conditions: Chills, disease progression, irritability, oedema peripheral, thirst

Hepatobiliary disorders: Cholecystitis acute, gallbladder polyp, hepatic function abnormal

Infections and infestations: Pharyngitis, pharyngotonsillitis, rhinitis, tinea versicolour, tonsillitis

Injury, poisoning and procedural complications: Fall, procedural dizziness, procedural headache

Investigations: Blood cortisol decreased, blood immunoglobulin E increased, blood insulin increased, blood triglycerides increased, creatinine renal clearance increased, electrocardiogram T wave amplitude decreased, blood corticotrophin increased, hepatic enzyme increased, international normalised ratio increased, liver function test abnormal, thyroxine free decreased, ultrasound biliary tract abnormal

Metabolism and nutrition disorders: Dyslipidaemia, fluid retention, food intolerance, lipomatosis, vitamin B complex deficiency

Musculoskeletal and connective tissue disorders: Muscle contracture, muscle spasms, musculoskeletal chest pain, pain in extremity

Nervous system disorders: Dizziness postural, paresthesia, presyncope, sensory disturbance

Psychiatric disorders: Anxiety, mood altered

Renal and urinary disorders: Micturition urgency, nocturia, pollakiuria, renal impairment

Skin and subcutaneous tissue disorders: Acanthosis nigricans, acne, cutaneous lupus erythematosus, dermatitis acneiform, eczema, erythema rash pruritic

Vascular disorders: Hot flush

Abnormal Hematologic and Clinical Chemistry Findings

Liver enzymes
Elevations in liver enzymes have been reported in healthy subjects and patients receiving pasireotide in clinical studies. Eight patients (5.1%) had elevations of ALT or AST >3xULN. Four 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. Liver function test results returned to baseline values after discontinuation of treatment (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Pancreatic enzymes
Based on adverse event reporting in patients receiving pasireotide in clinical studies, elevations were observed in lipase and amylase (7.5% and 2.5%, respectively). All elevations in amylase were low Common Terminology Criteria for Adverse Events v.3.0 (CTC) grade; out of 12 patients who had an increase in lipase, 3 of them had elevations > 2.0 and ≤ 5.0 x ULN (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

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. Newly occurring or worsening in lab abnormality for FPG was found in 112 out of 155 evaluable patients (72.2%).

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 (± range) 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 (4.6-5.6)	6.50 (5.2-7.8)	5.22 (4.7-5.6)	6.75 (5.4-9.6)
Pre-diabetic patients (n= 38)	5.77 (5.0-6.3)	7.45 (5.8-11.1)	5.71 (4.7-6.2)	7.13 (5.9-8.0)
Diabetic patients (n= 54)	6.50 (4.9-8.2)	7.95 (5.4-12.4)	6.42 (5.0-9.1)	8.30 (6.5-10.9)

Mean fasting plasma glucose (FPG) levels commonly increased within the first month of treatment, and mostly stabilized with the addition of anti-diabetic therapy in subsequent months. Patients with baseline HbA1c ≥7% or who were taking anti-diabetic medications prior to randomization tended to have higher mean changes in fasting plasma glucose and HbA1c relative to other patients. Following SIGNIFOR discontinuation, mean fasting plasma glucose and HbA1c values generally decreased over one month, 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. One case of ketosis and one case of ketoacidosis have been reported during use of SIGNIFOR.

Monitoring of blood glucose levels in patients is required prior to and during treatment with SIGNIFOR (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS**).

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been derived from post-marketing experience with SIGNIFOR. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Metabolism and nutrition disorders: Diabetic ketoacidosis.
Hepatobiliary Disorders: Cholangitis

DRUG INTERACTIONS

Overview

Caution is required when co-administering SIGNIFOR with drugs that are known to have hepatotoxic potential, or with anti-arrhythmic medicines and other drugs that may prolong the QT interval (see **WARNINGS AND PRECAUTIONS**). Medications that may disrupt electrolyte levels should be avoided when using SIGNIFOR.

In vitro **assessment of drug interactions*:*** 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 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 OAT1 or OAT3, OATP 1B1 or 1B3, and OCT1 or OCT2, efflux transporter P-gp, BCRP, MRP2 (multi-drug resistance protein 2) or BSEP (bile salt export pump).

Drug-Drug Interactions

General: The lists below of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, decrease heart rate, prolong the PR interval, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Effects of Other Drugs on SIGNIFOR

QTc-Prolonging Drugs: The concomitant use of SIGNIFOR with another QTc-prolonging drug should be avoided (see **WARNINGS AND PRECAUTIONS - Cardiovascular** and **Monitoring and Laboratory Tests**; **ADVERSE REACTIONS**; **ACTIONS AND CLINICAL PHARMACOLOGY - Cardiac Electrophysiology**). Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

- Class IA, III and IC antiarrhythmics
- Antipsychotics

- Antidepressants
- Opioids
- Macrolide antibiotics and analogues
- Quinolone antibiotics
- Antimalarials
- Azole antifungals
- Dopamine receptor antagonists
- Serotonin (5-HT_3) receptor antagonists
- Tyrosine kinase inhibitors
- Histone deacetylase inhibitors
- Beta-2 adrenoceptor agonists.

Drugs that Decrease Heart Rate and/or Prolong the PR Interval: SIGNIFOR results in a decrease in heart rate and an increase in the PR interval (see **WARNINGS AND PRECAUTIONS - Cardiovascular** and **Monitoring and Laboratory Tests**; **ADVERSE REACTIONS - Electrocardiography; ACTIONS AND CLINICAL PHARMACOLOGY - Cardiac Electrophysiology)**. The concomitant use of SIGNIFOR with other drugs that lower heart rate and/or prolong the PR interval, including, but not limited to, antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, alpha$_2$-adrenoceptor agonists, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and HIV protease inhibitors, should be avoided.

P-gp Substrate Interactions: Pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein) but is not an inducer of P-gp.

The influence of a P-gp inhibitor on the pharmacokinetics of subcutaneous pasireotide (600 μg, single dose) was tested in a drug-drug interaction study with co-administration of verapamil sustained release formulation (SR) (240 mg, multiple dose) in healthy volunteers. No change in the rate of pasireotide absorption and elimination or extent of exposure following concomitant administration with verapamil SR was observed. However grade 3 neutropenia, grade 3 lymphopenia, as well as grade 4 lipase and creatine phosphokinase (CPK) increase were observed in some subjects on co-administration. Co-administration of pasireotide with non-dihydropyridine calcium channel blockers such as verapamil should be avoided because of the risk of pharmacodynamic interactions affecting atrioventricular conduction (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

The potential for other strong P-gp inhibitors such as ketoconazole, cyclosporine, clarithromycin, to increase concentrations of pasireotide is unknown.

Effect of SIGNIFOR on Other Drugs

The use of SIGNIFOR with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B and high dose corticosteroids.

Anticoagulants: The safety of the combination of SIGNIFOR with anticoagulants has not been established. Coagulation parameters should be monitored regularly and the anticoagulant dose should be revised accordingly (see **WARNINGS AND PRECAUTIONS**).

Anti-Diabetics/Insulin: Dose adjustments (decrease or increase) of insulin and anti-diabetic products may be required when administered concomitantly with pasireotide (see **WARNINGS AND PRECAUTIONS**).

Bromocriptine: Coadministration of SIGNIFOR with bromocriptine may increase the blood levels of bromocriptine. Dose reduction of bromocriptine may be necessary.

Cyclosporine: Concomitant administration of cyclosporine with SIGNIFOR may decrease the relative bioavailability of cyclosporine. Therefore consider monitoring and dose adjustment of cyclosporine to maintain therapeutic levels.

Cytochrome P450/3A4 Interactions: Somatostatin analogs might have an indirect effect in decreasing the metabolic clearance of compounds metabolized by cytochrome P450 (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).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
SIGNIFOR has no or negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue or headache during treatment with SIGNIFOR.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended initial dose of SIGNIFOR is 0.6 mg by subcutaneous (s.c.) injection twice a day. Patients should be evaluated for treatment response (Normalization or >50% decrease 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 UFC reduction is typically seen by two months of treatment. 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 do not experience clinical benefit from SIGNIFOR after two months of

treatment should be considered for discontinuation. Individualized dose reduction may be considered for patients with a stable response.

Management of suspected adverse reactions may require a dose reduction of SIGNIFOR. The dose may be decreased, either temporarily or permanently, by 0.3 mg decrements. Efficacy should be monitored closely as there are limited data with the use of the 0.3 mg dose.

Prior to the start of SIGNIFOR, patients should have the following baseline evaluations (see **WARNINGS AND PRECAUTIONS**):

- Fasting Plasma Glucose
- Hemoglobin A1c
- Liver tests
- Electrocardiogram
- Gallbladder ultrasound

SIGNIFOR is contraindicated in patients with uncontrolled diabetes mellitus (see **CONTRAINDICATIONS**).

Special populations

Renal impairment:
No dose adjustment is required in patients with impaired renal function. In a clinical study of single dose pasireotide s.c, 900 µg, grade 3 and grade 4 increases in amylase, lipase and uric acid and grade 3 decreases in hemoglobin were observed in subjects with severe renal impairment and ESRD. SIGNIFOR should be used with caution in patients with severe renal impairment and ESRD (see **WARNINGS AND PRECAUTIONS - Renal**, **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**, **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic impairment:
Dose adjustment is not required in patients with mildly impaired hepatic function (Child-Pugh A). SIGNIFOR is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS**).

Pediatric patients (< 18 years of age):
SIGNIFOR should not be used in pediatric Cushing's disease patients (see **INDICATIONS AND CLINICAL USE** and **WARNINGS AND PRECAUTIONS – Special Populations**).

Geriatric patients (≥ 65 years of age):
There are limited data on the use of SIGNIFOR in patients 65 years and older. Generally, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Missed Dose

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.

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).

OVERDOSAGE

Doses up to 2.1 mg twice a day have been used in healthy volunteers with adverse reactions including diarrhea and QT prolongation.

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. Electrocardiogram monitoring is recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pasireotide is a novel cyclohexapeptide, injectable somatostatin analogue. 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. Corticotroph tumour cells from Cushing's disease patients frequently over-express SSTR5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels (SSTR1 and SSTR2). Pasireotide binds with high affinity to four of the five SSTRs: SSTR5 > SSTR2 > SSTR3 > SSTR1. Binding of pasireotide to corticotroph SSTR in ACTH producing adenomas results in inhibition of ACTH secretion.

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.

In vitro studies have shown that corticotroph tumour cells from Cushing's disease patients display a high expression of SSTR5 whereas the other receptor subtypes are either not expressed or are expressed at lower levels. Pasireotide binds and activates the SSTR of the corticotrophs in ACTH producing adenomas resulting in inhibition of ACTH secretion. The high affinity of pasireotide for four of the five SSTRs, especially to SSTR5, provides the basis for pasireotide to be an effective treatment for Cushing's disease patients.

Cardiac Electrophysiology

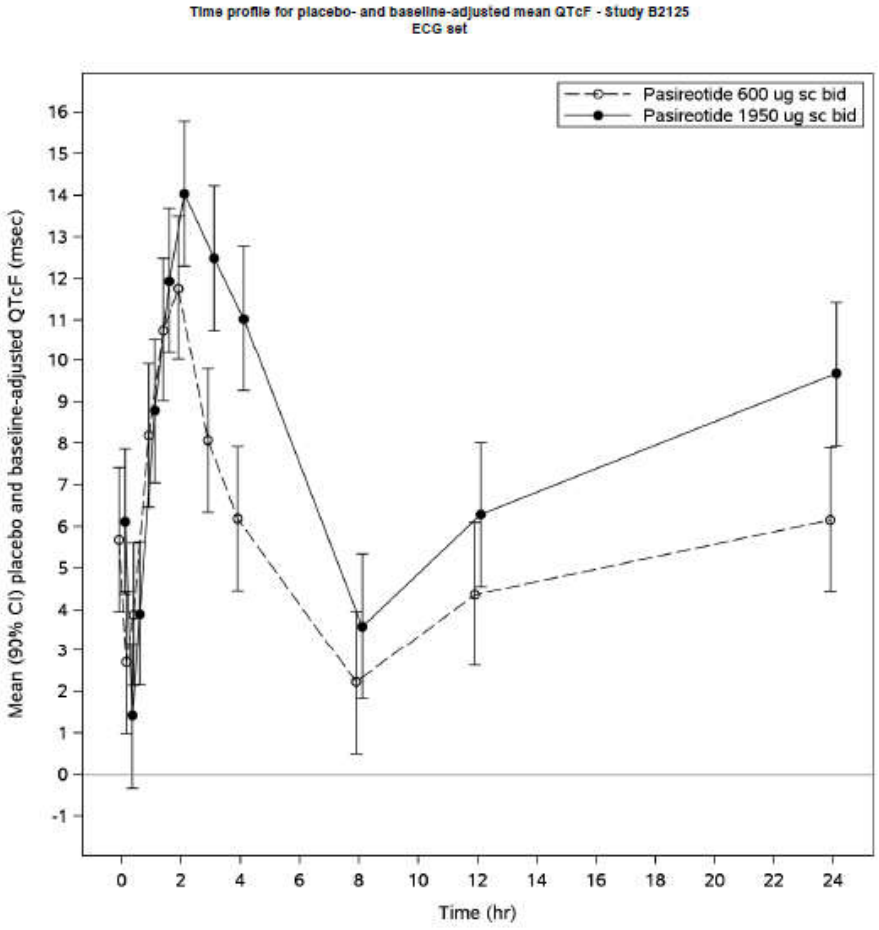
The effects of pasireotide (administered as SIGNIFOR s.c.) on cardiac electrophysiology were assessed in two dedicated ECG assessment studies (see **WARNINGS AND PRECAUTIONS - Cardiovascular** and **Monitoring and Laboratory Tests**; **ADVERSE REACTIONS**; **DRUG INTERACTIONS**).

ECG Study 1: In the first randomised, double-blind, placebo-controlled, crossover ECG assessment study, healthy volunteers (N=77) received treatment for 4 days with a supratherapeutic dose of SIGNIFOR 1950 µg administered twice a day, followed by a 1950 µg morning dose on day 5. ECG assessments were performed at 10 time points on day 5. SIGNIFOR 1950 µg treatment was associated with statistically significant decreases in heart rate and prolongation of the Fridericia-corrected QT interval ($QTcF=QT/RR^{0.33}$) at all timepoints on day 5. The maximum placebo-adjusted mean changes from baseline ($\Delta\Delta$QTcF) occurred at 2 h post-dosing and were -12.6 bpm (90% CI -13.9, -11.3) for heart rate and 17.5 ms (90% CI 15.5, 19.4) for the QTcF interval. SIGNIFOR 1950 µg treatment was also associated with statistically significant increases in the PR interval, with a maximum placebo-adjusted mean change from baseline of 6.9 ms (90% CI 5.4, 8.5) at 4 h post-dosing.

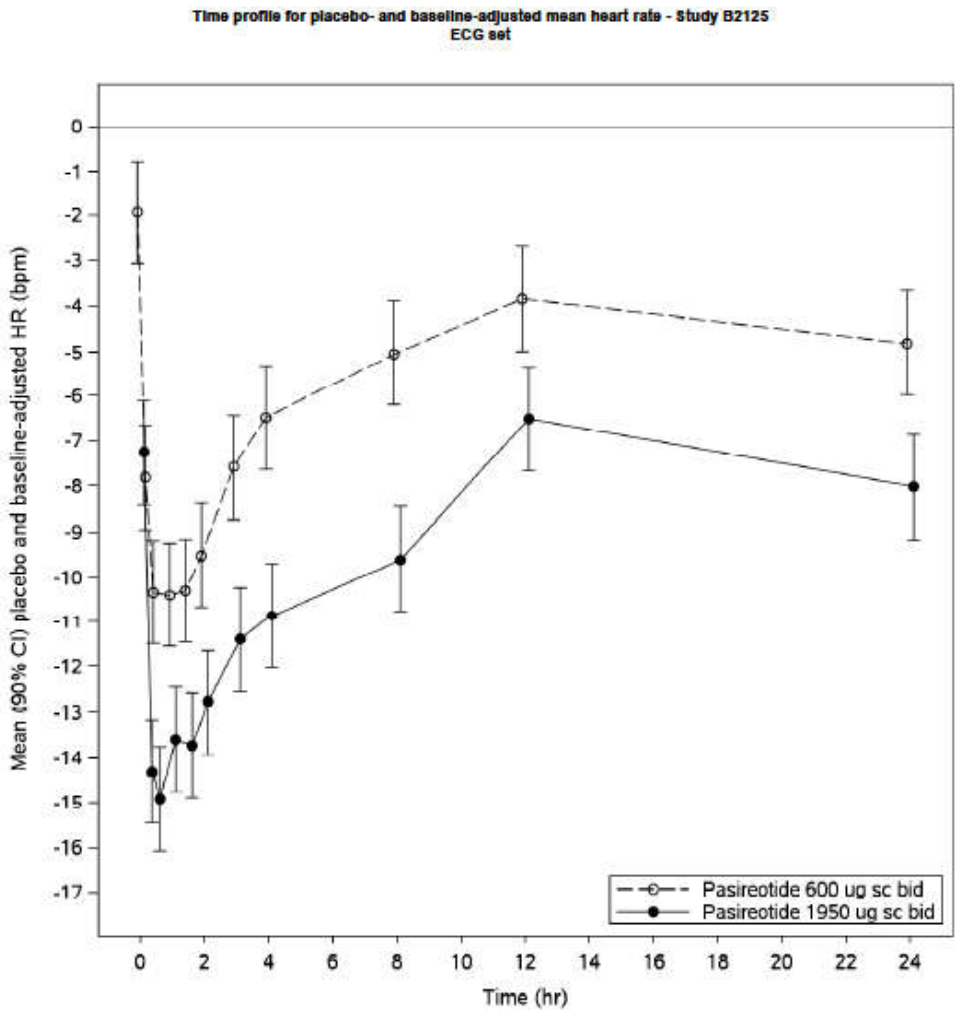
ECG Study 2: In a second randomised, double-blind, placebo-controlled, crossover ECG assessment study in healthy volunteers (N=105), subjects received treatment for 4 days with a therapeutic dose of SIGNIFOR 600 µg twice a day and a supratherapeutic dose of SIGNIFOR 1950 µg twice a day, followed by 600 µg and 1950 µg morning doses on day 5. ECG assessments were performed at 11 time points on day 5.

In both the 600 µg and 1950 µg treatment arms, SIGNIFOR was associated with statistically significant QTcF prolongation at all timepoints on day 5. The maximum placebo-adjusted mean change from baseline occurred at 2 h post-dosing in both treatment arms and was 11.8 ms (90% CI 10.0, 13.5) in the 600 µg treatment arm and 14.0 ms (90% CI 12.3, 15.8) in the 1950 µg arm.

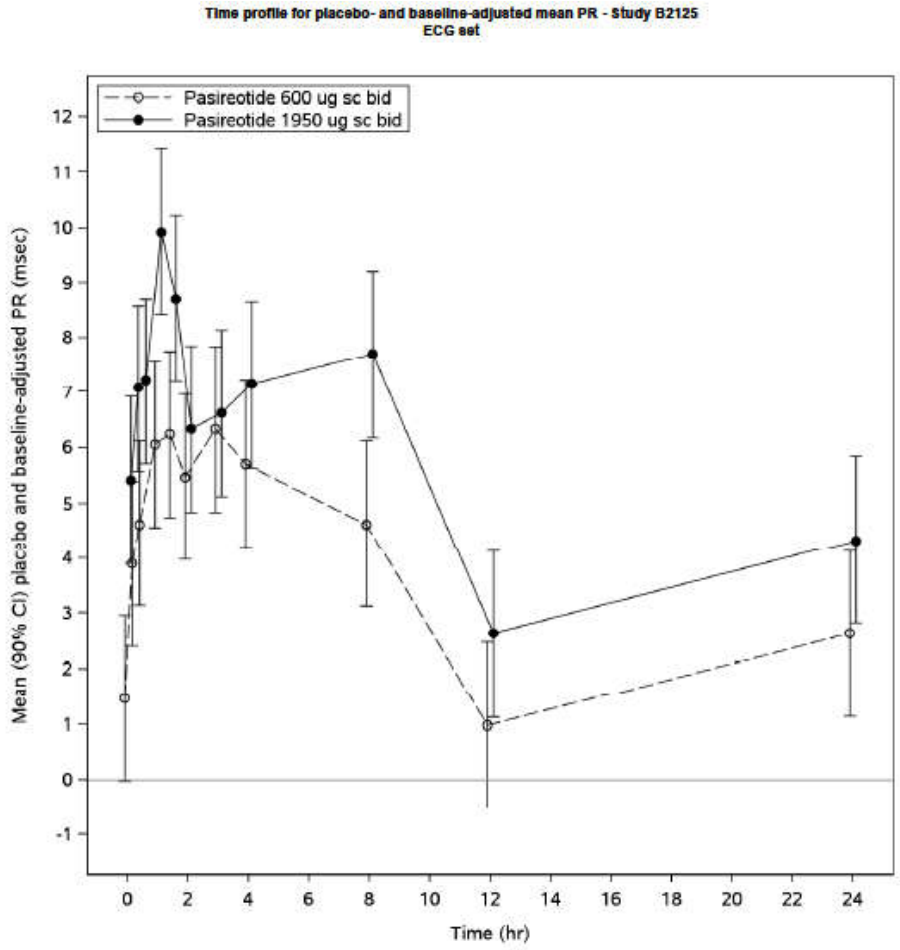
The mechanism for the observed QT prolongation is not known.



In both the 600 µg and 1950 µg treatment arms, SIGNIFOR was associated with statistically significant reductions in heart rate at all timepoints on day 5. The maximum placebo-adjusted mean change from baseline was -10.4 bpm (90% CI -11.5, -9.2) at 1 h post-dosing in the 600 µg treatment arm and -14.9 bpm (90% CI -16.1, -13.8) in the 1950 µg arm.



Statistically significant prolongation of the PR interval occurred from 0.25 to 8 h post-dosing in the SIGNIFOR 600 µg arm and at all timepoints in the SIGNIFOR 1950 µg arm on day 5. The maximum placebo-adjusted mean change from baseline occurred at 2 h post-dosing in both treatment arms and was 6.1 ms (90% CI 4.6, 7.6) in the 600 µg arm and 9.9 ms (90% CI 8.4, 11.4) in the 1950 µg arm.



On the basis of population pharmacokinetic modelling, the median steady-state C_{max} of pasireotide in patients with Cushing's disease is predicted to be 48 ng/mL for the 600 µg dose and 58 ng/mL for the 900 µg dose, both administered twice a day. In ECG Study 1, the median C_{max} for pasireotide 1950 µg twice a day in healthy volunteers was 64 ng/mL. In ECG Study 2, the median C_{max} values were 23 ng/mL for pasireotide 600 µg twice a day and 78 ng/mL for pasireotide 1950 µg twice a day.

Pharmacokinetics

Table 3 Summary of SIGNIFOR (twice a day dosing) Pharmacokinetic Parameters in Cushing's Disease Patients

Dose (µg)	$C_{min,ss}$ (ng/mL)*	$C_{max,ss}$ (ng/mL)*	$T_{max,ss}$ (hr)**	$AUC_{0-8,ss}$ (hr*ng/mL) *
600	4.9 ± 2.6	21.3 ± 6.9	2	99.7 ± 33.8

**Data expressed as mean (SD) values from day 15;*
***Data expressed as median value from day 15.*

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. In Cushing's disease patients

following 600µg twice a day, s.c. dosing for 15 days, the steady-state was achieved within 5 days.

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

No clinical studies were performed to evaluate the effect of food on pasireotide administration.

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.

Metabolism: Pasireotide was shown to be highly metabolically stable. In healthy volunteers, pasireotide, in its unchanged form, is predominantly found in plasma, urine and feces.

Excretion: 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 a single dose of 600 µg 55.9 ± 6.63% of the radioactivity dose was recovered over the first 10 days after pasireotide administration, including 48.3 ± 8.16% of the radioactivity in feces and 7.63 ± 2.03% in urine.
Pasireotide demonstrates low clearance (CL/F, ~ 7.6 litres/h for healthy volunteers and ~3.8 litres/h for 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.

Steady-State Pharmacokinetics, Linearity and Accumulation: In Cushing's disease patients following 600 µg twice a day, s.c. dosing for 15 days, the steady-state was achieved within 5 days. In Cushing's disease patients, pasireotide demonstrates linear pharmacokinetics in a dose range from 0.3 to 1.2mg twice a day, based on $C_{min,ss}$, whereas the pasireotide pharmacokinetics was linear between 0.0025 to 1.5mg, in healthy volunteers. The accumulation (ratio of 1.9) of pasireotide was moderate in Cushing's disease patients.

Special Populations and Conditions

Pediatrics (< 18 years of age): No studies have been performed in pediatric patients.

Geriatrics (≥ 65 years of age): 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.

Gender: Population PK analyses of SIGNIFOR suggest that gender does not influence PK parameters.

Race: Population PK analyses of SIGNIFOR suggest that race does not influence PK parameters.

Age: 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 111% 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.

Hepatic Impairment: SIGNIFOR is contraindicated in patients with moderate or severe hepatic impairment (see **CONTRAINDICATIONS**). In a clinical study with single dose administration of 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.

Renal Impairment: No dose adjustment is required in patients with impaired renal function. SIGNIFOR should be used with caution in patients with severe renal impairment.

In a clinical study with single dose administration of 900 μg pasireotide as SIGNIFOR s.c. in subjects with impaired renal function, the degree of renal impairment did not have a significant impact on the pharmacokinetics of pasireotide. The $AUC_{0\text{-}inf}$ decreased by 22% , 14% and 1% for mild, moderate and severe renally impaired subjects and increased by 25% in ESRD subjects compared to normal subjects adjusted for age, gender and weight as covariates. The Cmax decreased by 28%, 23%, 19% and 10% for mild, moderate, severe renally impaired and ESRD subjects compared to normal subjects adjusted for age, gender and weight as covariates. However, increases in unbound pasireotide $AUC_{inf,u}$ of 1.85, 2.41, 2.96 fold and Cmax,u of 1.36, 2.00, 3.01 fold were observed in patients with moderate, severe renal impairment and ESRD. Grade 3 and Grade 4 increases in amylase, lipase and uric acid and grade 3 decreases in hemoglobin were also observed in subjects with severe renal impairment and ESRD. Hence, SIGNIFOR should be used with caution in patients with severe renal impairment and ESRD (see **WARNINGS AND PRECAUTIONS – Renal**, **WARNINGS AND PRECAUTIONS - Monitoring and laboratory tests**, **DOSAGE AND ADMINISTRATION**).

Lean Body weight: Lean 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_{ss} 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.

Genetic polymorphism: The effects of genetic polymorphisms on the pharmacokinetics of SIGNIFOR have not been established.

STORAGE AND STABILITY

Store at room temperature (15°C – 30°C).

Store in original package (in order to protect from light).

SIGNIFOR (pasireotide injection) must be kept out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

The solution is supplied in a 1 mL one point-cut colorless hydrolytic class I (Ph. Eur., USP) glass ampoule.

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 (pasireotide injection) ampoule. For instructions on the use of SIGNIFOR (pasireotide injection) ampoules, refer to the **CONSUMER INFORMATION** section.

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

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

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SIGNIFOR (pasireotide injection) solution is available in three strengths. Each ampoule 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).

SIGNIFOR is available in packs containing 6 and 60 ampoules.

Non-medicinal Ingredients; Mannitol, sodium hydroxide, tartaric acid, water for injections.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Pasireotide diaspartate

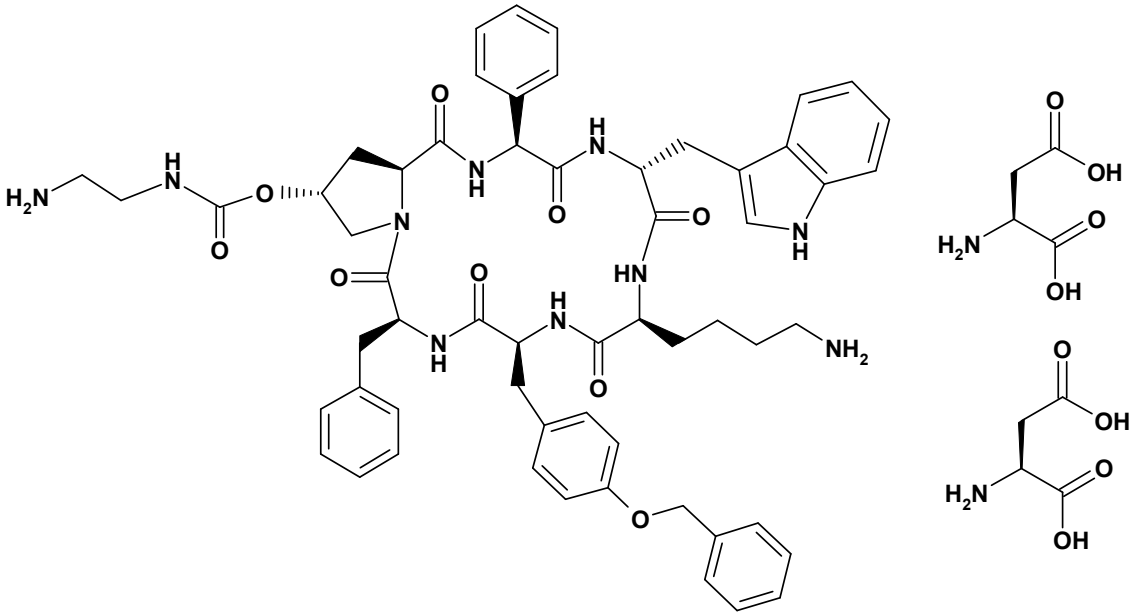
Chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt

Molecular formula and molecular mass: $C_{58}H_{66}N_{10}O_9 \cdot 2\ C_4H_7NO_4$

1047.206 + 266.205 = 1313.41

Salt/base ratio: 1.254

Structural formula:



Physicochemical properties: Pasireotide diaspartate, a novel cyclohexapeptide, is a somatostatin analogue. It is a white to slightly greyish powder (lyophilisate).

The aqueous ionization constants (pKa) of pasireotide were determined by potentiometric titration in water/dioxane in 0.15 M KCl at 25°C. The values are: pKa1 = 10.2, pKa2 = 9.1. At 25°C, the solubility of pasireotide is >100 mg/mL in water.

CLINICAL TRIALS

Study demographics and trial design

A phase III, multicenter, randomised study was conducted to evaluate the safety and efficacy of two dose levels of SIGNIFOR over a 6month 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 dose of either 0.6 mg s.c. twice a day or 0.9 mg s.c. twice a day 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 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. The dosage can be reduced by 0.3mg s.c. twice a day at any time during the study for intolerability. 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%) despite pituitary surgery and few patients (≤5%) in either treatment group had received previous pituitary irradiation. The median exposure to the treatment was 10.4 months (0.03-37.8) with 68% of patients having at least 6 months.

Baseline characteristics were balanced between the two randomised 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 twice a day group and 782 nmoL/24hr for the 0.9 mg twice a day group); normal range 30 to 145 nmoL/24 hr).

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 randomised dose) during this period.

During the pivotal trial, 62% of patients with normal HbA1c (<6%) at baseline became either pre-diabetic or diabetic. HbA1c levels stabilized with the addition of antihyperglycemic treatment, but did not return to baseline values.

Study results

Primary Endpoint: Normalization of UFC
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 randomised to pasireotide 0.6 mg twice a day and 0.9 mg twice a day, respectively. Over half of responders (55.6%) at month 6 were also responders at month 12.

A supportive efficacy analysis was conducted in which patients were further classified into the response category partial responder (UFC >1.0 x ULN but with a reduction in UFC ≥50% compared to baseline). Up-titration at month 3 is allowed for 0.6mg dose group but not 0.9mg dose group. The total proportion of full or partial responders at month 6, constituted 33% and

37% (0.6 mg twice a day and 0.9 mg twice a day, respectively) of the randomised patients (Table 4). Patients uncontrolled at both Months 1 and 2 were likely (90%) to remain uncontrolled at Months 6 and 12.

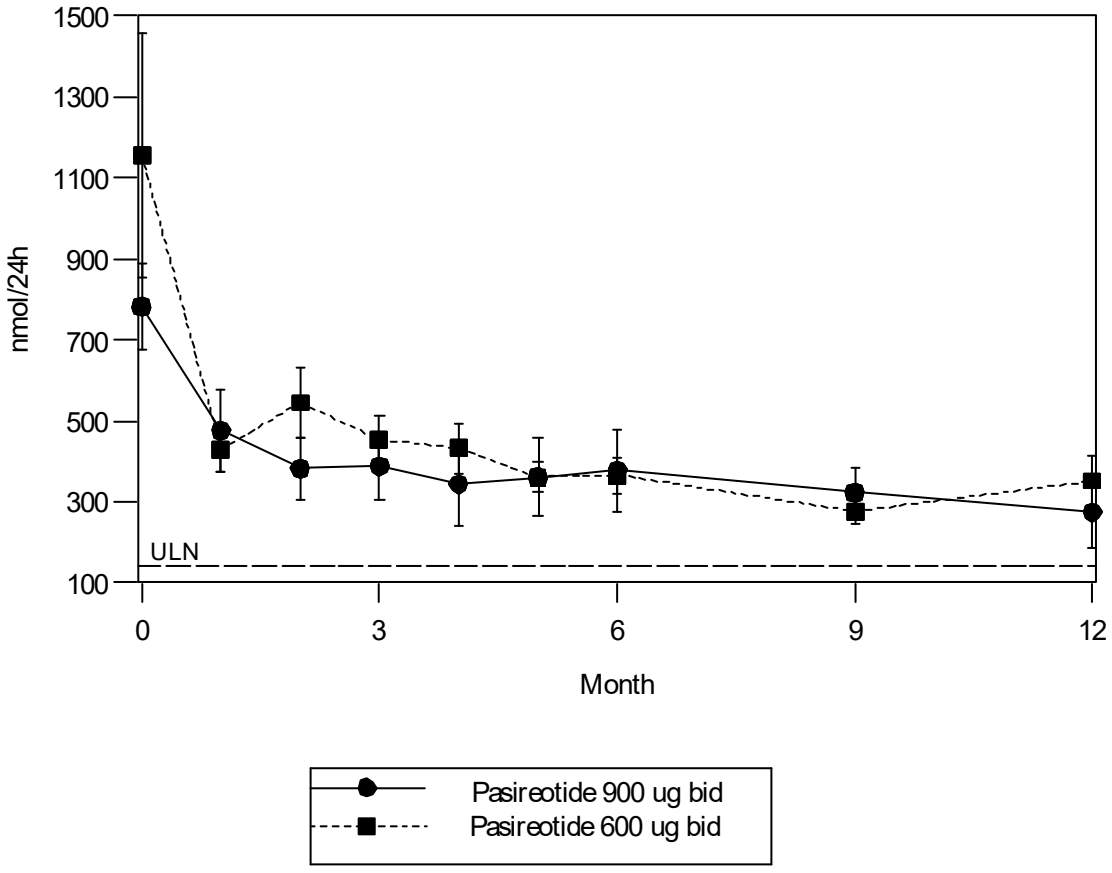
Table 4 Response rates at month 6 per randomised dose group

Response category	Pasireotide 0.6 mg b.i.d. (N=82) n (%)	Pasireotide 0.9 mg b.i.d.(N= 80) n (%)
Responder	12 (14.6%)	21 (26.3%)
Partial responder	15 (18.3%)	9 (11.2%)
Non-responder	55 (67.1 %)	50 (62.5%)

Responder: fully controlled (UFC ≤1.0 x ULN) without up-titration at month 3; Partial responder: UFC >1.0 x ULN but with a reduction in UFC ≥50% compared to baseline. Up-titration at month 3 is allowed for 0.6mg dose group but not 0.9mg dose group; non-responder: neither a responder nor a partial responder.

In both dose groups, SIGNIFOR resulted in a 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.

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



Note: The reference line is the upper limit normal for UFC, which is 145 nmoL/24h.+/-Standard errors are displayed.

Decreases were also demonstrated by the overall percentage of change in the mean UFC levels at month 6 and 12 as compared to baseline values (Table 5).

Table 5 Percentage change in mean UFC levels per randomised 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)

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

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

In vitro pharmacology

Corticotroph tumour cells from Cushing's disease patients express high levels of SSTR5. Other receptor subtypes (SSTR 1-4) are either not expressed or are expressed at lower levels. Pasireotide is a somatostatin analogue with high binding affinity and high functional activity for somatostatin receptor subtypes SSTR 1, 2, 3 and 5. The high affinity of pasireotide for four of the five SSTRs, especially to SSTR5, provides the basis for pasireotide's mechanism of action. In a primary mouse ACTH secreting pituitary cell line, pasireotide inhibited the release of ACTH with high potency (IC_{50} 0.2 nmol/L). Similarly, pasireotide inhibited release of ACTH secretion from human corticotroph adenoma cells.

In vivo pharmacology

In vivo studies showed a strong inhibitory effect of pasireotide on ACTH and corticosterone secretion in rats pre-treated with corticotropin-releasing hormone.

Nonclinical Pharmacokinetics

Pasireotide is well absorbed after s.c. dosing in all species tested with complete bioavailability. The plasma protein binding is moderate across species with the lowest binding in human (88%); therefore a substantial change in drug kinetics due to protein binding changes is not expected. Pasireotide and/or its metabolites in tissues were eliminated slowly and were mainly distributed to the adrenal cortex, kidney cortex, bone marrow, blood vessel wall, lymph nodes, spleen, and liver while showing minimal brain penetration and no specific retention in melanin-rich tissues (uveal tract and skin). Pasireotide and/or its metabolites showed some distribution to the fetus in rats and rabbits. The transfer of pasireotide-related radioactivity into milk was observed in rats.

Clinical Pharmacology

Clinical Pharmacokinetics (PK)

In healthy volunteers, following a single s.c. injection between 2.5 - 1500 µg, pasireotide pharmacokinetics demonstrated fast absorption, extensive distribution, low clearance, and long half-life. The PK exposures (C_{max} and AUC_{inf}) were approximately dose-proportional for single

(2.5 – 1500 µg) and multiple doses (50- 600 µg). The drug was rapidly absorbed with a median T_{max} of 0.25-0.5 hr post dose. The disposition phase of the mean plasma concentration-versus-time profiles of pasireotide appeared to be tri-exponential for doses of 600-1500 µg. The apparent effective half-life ($t_{1/2}$) was estimated to be ~12 hours. Pasireotide is primarily distributed in the plasma (91%) with a large apparent volume of distribution (V_z/F) >100 L. Pasireotide is metabolically stable and is found in its unchanged form in plasma, urine and feces. Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution from the renal route. The clearance (CL/F) of pasireotide in healthy volunteers and Cushing's disease patients is ~ 7.6 liters/h and ~3.8 litres/h, respectively. Following 50- 600 µg q.d. dosing of pasireotide s.c. in healthy volunteers, the steady-state was achieved within 3 days. The accumulation to steady-state was found to be moderate (approximately 20-40%) (see **ACTION AND CLINICAL PHARMACOLOGY**).

TOXICOLOGY

Safety pharmacology

The cardiovascular safety of pasireotide was evaluated using *in vitro* methods (hERG assay, Purkinje fiber assay, effect of pasireotide on potassium channel currents, effect of pasireotide on sodium and calcium channel currents) and in an *in vivo* conscious monkey telemetry study (single s.c. doses of 0.4, 0.8 and 1.6 mg/kg). *In vitro,* a statistically significant, concentration-dependent hERG current block was observed at 13 and 39 µg/mL (8.2% and 16.8% inhibition, respectively). These concentrations are 448 and 1345 times human C_{max} at 900 µg bid, respectively. There were no other findings. *In vivo,* a NOAEL of 1.6 mg/kg was obtained.
The effect of pasireotide on respiratory function and neurobehaviour was assessed in rats (single s.c. doses of 0.8, 1.6 and 4.0 mg/kg) and mice (single s.c. doses of 0.4, 1.2, 4.0 and 12 mg/kg), respectively. Toxicologically significant effects were not observed.

Single dose toxicity

The acute toxicity of pasireotide was assessed in rats and mice at 15 and 30 mg/kg by the s.c. route. Lethalities were not observed.

Repeated dose toxicity

Rats

The pivotal rodent repeat-dose toxicity study was conducted in male and female rats. Animals were administered pasireotide by s.c. injection once daily at 0.0008, 0.024, 0.08 and 0.24 mg/kg/day for 26 weeks. When compared with human AUC values, these dose levels provide an exposure margin of 0.07, 0.24 (0.33 and 0.15 for males and females, respectively), 0.49, 1.92, respectively. The NOAEL was considered to be 0.024 mg/kg/day based on histological alterations in the pituitary (males) and the genital tract (females).

All pasireotide-mediated effects were considered to be a result of the drug's pharmacology and all changes demonstrated reversibility following a drug-free period. Decreased body weight was observed in males (from 0.008 mg/kg) and females (0.24 mg/kg). In males, decreased pituitary weight and decreased cytoplasmic mass of acidophile cells/somatotrophs was observed at doses >0.024 mg/kg. In females, alterations in the genital tract (decreased number of corpora lutea,

vaginal mucosal hyperplasia or hypertrophy of mucification, vaginal hypertrophy) consistent with prolongation of the estrous cycle were observed at doses ≥ 0.08 mg/kg.

Inhibitory effects on lymphoid and hematopoietic organs were observed and included decrease thymus weight and cellularity as well as decreased hematopoietic activity of the spleen and bone marrow. A lack of new bone formation beneath the epiphyseal plate of the tibia and femur was observed. Serum biochemistry changes (increased ALT, decreased albumin) and decreased liver weight suggested possible effects on the liver at high dose levels, possibly as a secondary result to the decrease in IGF-1. Changes in coagulation parameters (increased PT and APTT) noted in females are likely related to the pharmacologic effect of pasireotide, probably through modification of the liver production of coagulating factors regulated by GH.

Monkeys
The pivotal non-rodent repeat-dose toxicity study was conducted in male and female monkeys. Animals were administered pasireotide at 0.4, 1.6, and 3.2 mg/kg/day for 39 weeks. When compared with human AUC values, these dose levels provide an exposure margin of 12.2, 39.0 and 96.1 for males, and 13.3, 54.7 and 102.6 for females**.** The NOAEL was considered to be 1.6 mg/kg/day based on histological alterations in the pituitary (increased acidophilia in the pars distallis), thyroid (small follicles), large intestine (distension with firm fecal material) and injection site reactions.
All pasireotide-mediated effects were considered to be a result of the drug's pharmacology and all changes demonstrated reversibility following a drug-free period.

Genotoxicity
Pasireotide did not exhibit mutagenic or clastogenic potential in a battery of assays including the Ames test, human peripheral lymphocyte chromosome aberration test, or the *in vivo* rat micronucleus test.

Carcinogenicity
The carcinogenic potential of pasireotide was assessed by the s.c. route in the 26-week transgenic RasH2 mouse model (dose levels: 0, 0.5, 1.0, 2.5 mg/kg/day) and the 2-year rat bioassay (dose levels: 0, 0.01, 0.05, 0.3 mg/kg/day). Pasireotide was not carcinogenic in either model.

Reproductive and Developmental Toxicity
Fertility and early embryonic development was evaluated in rats. Pasireotide was administered by s.c. injection at 0.1, 1.0 and 10 mg/kg/day prior to mating, during mating and through gestation day (GD) 6. Reproductive effects were observed in females only and included prolonged estrus cycles/acyclicity at doses ≥ 1.0 mg/kg and decreased numbers of corpora lutea, implantation sites, and/or viable fetuses at all doses. A NOAEL for female fertility was not established (<0.1 mg/kg/day).

Embryo-fetal development was evaluated in rats and rabbits. In rats, pasireotide was administered by s.c. injection at 1, 5 and 10 mg/kg/day from GD 6-17. At 10 mg/kg, and in the presence of maternal toxicity and mortality, effects on the F_1 generation were noted and consisted of increased early/total resorptions, decreased fetal weights, and mal-rotated limbs. The fetal NOAEL was 5 mg/kg. Pasireotide was not teratogenic in the rat.

In rabbits, pasireotide was administered by s.c. injection at 0.05, 1.0 and 5.0 mg/kg/day from GD 7-20. Maternal toxicity was observed from 1.0 mg/kg and mortality occurred at 5.0 mg/kg. Reproductive and fetal effects (increased early and/or total resorptions, decreased fetal weights) were noted in the presence of maternal toxicity at doses ≥ 1 mg/kg. At 5 mg/kg, abortions and a decreased number of viable fetuses were seen. Increased skeletal variations noted at 5.0 mg/kg were considered secondary to the reduced fetal weights. The maternal and fetal NOAEL were 0.05 mg/kg. Pasireotide was not teratogenic in the rabbit.

Pre- and post-natal development was evaluated in rats. Pasireotide was administered by s.c. injection at 2, 5 and 10 mg/kg/day to F_0 generation dams from GD 6 to day 21, 22 or 23 *post partum*. Maternal toxicity was observed at all doses and drug-related mortality was noted at 5 mg/kg. Maternal performance was unaffected by administration of pasireotide (no change in gestation index, length of gestation, numbers of live, dead pups, number of implantation scars, sex ratio and the live birth index). Lower F_1 body weights were seen at all doses. Secondary to the lower pup weights, the mean day of pinna unfolding was slightly increased in all dose groups. Post weaning, body weight gains were comparable for all groups demonstrating reversibility. There was no effect on visual function, physical development, behavioural performance, macroscopic findings, parental performance or uterine findings for the F1 generation adults.

Antigenicity

Antigenicity was not evaluated with the s.c. formulation. Using pasireotide LAR in a rat i.m. study, anti-pasireotide antibodies were detected in 26/59 treated animals. The antibodies were considered non-neutralizing as pharmacologic effects and drug levels were sustained.

Immunotoxicity

The immunotoxic potential of pasireotide was evaluated in a 4-week rat s.c. immunotoxicity study (dose levels: 0.08, 0.24 and 0.8 mg/kg/day). Pasireotide exhibits low immunotoxic potential. Although a slight decrease in lymphocytes counts was observed in males at 0.24 and 0.8 mg/kg/day (total lymphocyte counts and absolute counts of Total T lymphocytes, Helper T lymphocytes, Cytotoxic T lymphocytes, natural killer lymphocytes and B lymphocytes), there were no toxicologically-relevant pasireotide effects on immune function (anti-KLH IgM, anti-KLH IgG responses unaffected by pasireotide treatment).

Phototoxicity

In the absorption spectrum of pasireotide, a significant peak was found at around 360 nm. An *in vitro* phototoxicity assay was performed. Pasireotide did not exhibit phototoxic potential.

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PART III: CONSUMER INFORMATION

PrSIGNIFOR®
(Pasireotide injection)

This leaflet is part III of a three-part "Product Monograph" published when SIGNIFOR® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SIGNIFOR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is:

SIGNIFOR 0.3 mg, 0.6 mg and 0.9 mg solution for injection contains the active substance pasireotide, which is a synthetic compound derived from somatostatin.

What the medication is used for:

SIGNIFOR (pasireotide) is used in adults. It is a medicine to treat a disease called Cushing's. It is used when surgery is not an option or has not produced the required results. Cushing's disease is a condition caused by an enlargement of a part of the gland called the pituitary at the base of the brain, a so-called pituitary adenoma. This adenoma leads the body to make large amounts of a hormone called adrenocorticotropic hormone (ACTH).

SIGNIFOR should only be prescribed and supervised by a qualified doctor. To receive SIGNIFOR, you must be enrolled in the Access Program for SIGNIFOR.

What it does:

SIGNIFOR is a medicine containing a novel synthetic substance that mimics the action of somatostatin, a substance normally found in the human body, which can block the production of certain hormones, such as ACTH.

When it should not be used:

- If you are allergic to pasireotide or to any other ingredient in the medication or its container
- If you have moderate or severe liver problems
- If you have uncontrolled diabetes
- If you are pregnant
- If you are a woman of childbearing potential and not using contraception (birth control)
- If you are breastfeeding
- If you have heart problems

What the medicinal ingredient is:
Pasireotide diaspartate.

What the nonmedicinal ingredients are:
Mannitol, sodium hydroxide, tartaric acid, and water for injections.

What dosage forms it comes in:

SIGNIFOR is a solution supplied in an ampoule containing 1 mL of a clear, colourless solution.

Each ampoule contains 0.3 mg or 0.6 mg or 0.9 mg pasireotide (as pasireotide diaspartate).

SIGNIFOR is available in packs containing 60 ampoules.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious side effects include:
- Liver problems
- Heart problems (i.e. slow or irregular heart beat)
- Changes in blood glucose levels

BEFORE you use SIGNIFOR talk to your doctor or pharmacist if:

- You have problems with your blood sugar levels, either too high (hyperglycemia/diabetes) or too low (hypoglycaemia)
- You have problems with your liver
- You have severe kidney problems
- You have heart problems. This includes an abnormal heart rate or rhythm. This can also include problems with the electrical system of your heart called QT prolongation
- Take medicines to control your heart beat (antiarrhythmics) or medicines that may have an unwanted effect on the function of the heart beat (QT prolongation)
- You have a history of fainting spells
- You have low levels of pituitary hormones
- You have low levels of potassium or magnesium in your blood
- You have conditions such as vomiting, diarrhea, dehydration
- You have gallstones
- You are pregnant, may be pregnant or thinking or becoming pregnant. Your doctor will discuss whether you can become pregnant or not.
- You are breastfeeding. It is not known if SIGNIFOR passes into breast milk
- You take medicines to control your blood pressure (such as beta-blockers or calcium channel blockers)
- You take medicines to control electrolytes (potassium, magnesium) balance in your body
- You take medicines that affect how your blood clots

Your doctor may wish to check your blood sugar levels. You may need to start taking medicines to control your blood sugar levels or your doctor may adjust the medicines you are now taking to control your blood sugar levels.

Before your doctor prescribes SIGNIFOR, they should do tests including:

- Blood tests
- Liver tests

- Electrocardiogram, to measure the electrical activity of the heart
- Gallbladder ultrasound

These tests should be repeated during treatment.

Your doctor may wish to check your gallbladder, liver enzymes and pituitary hormones on a regular basis.

During your treatment with SIGNIFOR
Tell your doctor straight away if:

- You are feeling very weak
- You lose weight
- You have nausea or vomiting
- You have low blood pressure

Children and adolescents (under 18 years old)
SIGNIFOR is not to be used in children or adolescents.

To prevent pregnancy, female patients of childbearing potential should use adequate birth control.

Driving and Using Machines: Before you perform tasks which may require special attention, wait until you know how you respond to SIGNIFOR as fatigue or headache can occur.

INTERACTIONS WITH THIS MEDICATION

The following list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems while receiving SIGNIFOR. You should check with your doctor or pharmacist before taking any other medication with SIGNIFOR.

Drugs that may interact with SIGNIFOR include:

- Anti-arrhythmics used to treat irregular heart beat such as amiodarone, disopyramide, procainamide, quinidine, sotalol, ibutilide, dronedarone, flecainide, propafenone
- Medicines that may have an unwanted effect on the function of the heart (QT prolongation) such as:
  - antipsychotics (e.g., haloperidol, pimozide, droperidol, ziprasidone, chlorpromazine)
  - antidepressants (e.g., imipramine, citalopram, amitriptyline, maprotiline, venlafaxine)
  - methadone
  - antibiotics (e.g., clarithromycin, moxifloxacin, erythromycin, azithromycin, tacrolimus, levofloxacin, ciprofloxacin)
  - antimalarials (e.g., chloroquine, quinine)
  - antifungals (e.g., ketoconazole, fluconazole, voriconazole)
  - dopamine receptor antagonists (e.g. domperidone)
  - antiemetics (e.g., intravenous ondansetron)
  - cancer drugs (e.g., sunitinib, nilotinib, vandetanib, lapatinib, vorinostat)
- Asthma drugs (e.g., formoterol, salmeterol)
- Diuretics (water pills)
- Laxatives and enemas
- Amphotericin B
- High dose corticosteroids
- Medicines that decrease heart rate and prolong the PR interval:
  - antihypertensives (e.g., atenolol, diltiazem, verapamil, clonidine)
  - drugs to treat heart failure (e.g., digoxin)
  - drugs to treat multiple sclerosis (e.g., fingolimod)
  - drugs to treat HIV infection (e.g., atazanavir)
- Certain other medicines, such as cyclosporine, bromocriptine
- Medicines that work to prevent blood clots (anticoagulants)
- Antidiabetic drugs including insulin and oral medicines

This list includes some, but not all, of the drugs that may increase the risk of side effects while receiving SIGNIFOR. Tell your doctor or pharmacist if you are taking these or any other medicines even those not prescribed (including any over the counter drugs, vitamins, or herbal medicines).

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of SIGNIFOR is 0.6 mg injected under your skin (subcutaneous) two times a day (approximately every 12 hours). Using SIGNIFOR at the same time each day will help you remember when to use your medicine.

Your doctor will monitor how you respond to the treatment with SIGNIFOR and may ask you to change to a higher or lower dose.

How long to take SIGNIFOR
Your doctor will regularly check your condition to see if the treatment is working. You will need to take SIGNIFOR for as long as your doctor tells you. This is a long-term treatment, possibly lasting for years. If you stop your treatment your symptoms may come back.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Do not use a double dose of SIGNIFOR to make up for a forgotten dose. If you forgot to administer a dose of SIGNIFOR simply take your next injection at the scheduled time.

Instructions for use of SIGNIFOR

Your health care practitioner will have instructed you on how to use SIGNIFOR ampoules. However, before using the ampoule, please read the following information carefully. If you are not sure about how to give the injection or you have any questions, please ask your doctor, nurse or pharmacist for help.

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 the SIGNIFOR ampoules according to the storage condition listed on the box.

Important Safety Information

Caution: Keep the ampoule out of the reach of children

What you need, to give yourself a subcutaneous injection:
1. One SIGNIFOR ampoule
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 injections. 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 or 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 ampoule out of the box.
- Carefully inspect the ampoule. DO NOT USE if it is broken or if the liquid looks cloudy or contains particles. In all these cases, return the entire product pack to the pharmacy.

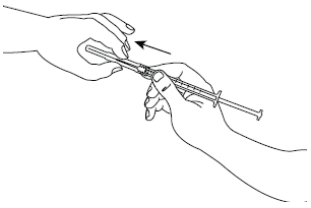
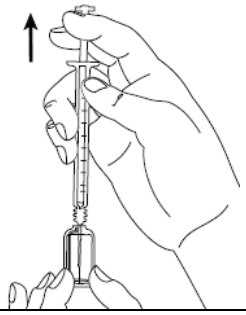
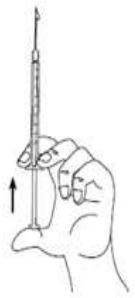
Ampoules should be opened just prior to administration, and any unused portion discarded.

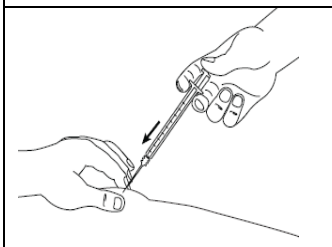
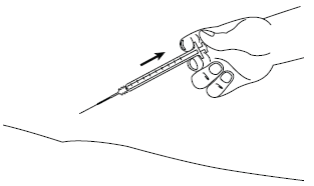
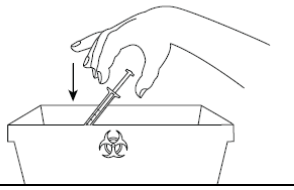
Check the expiry date and the dose:

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

DO NOT USE if the product has expired or if the dose is not the one you have been prescribed. In both cases, return the entire product pack to the pharmacy.

How to inject SIGNIFOR

	Step 1: SIGNIFOR solution for injection is filled in a break-off ampoule. The colored dot on the top part marks the position of the breaking cut on the neck of the ampoule. Tap the ampoule with your finger in order to make sure there is no liquid in the top part when you open the ampoule.
	The solution should be free of visible particles, clear and colorless. Do not use SIGNIFOR if the solution is not clear or contains particles.
	**Step 2**: Recommended procedure: hold the ampoule in an upright position with the colored dot facing away from you. Hold the base of the ampoule in one hand. Keeping your thumbs together above and below the neck, break off the top of the ampoule at the breaking cut. Once open, put the ampoule 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 ampoule and pull the plunger to draw the entire contents of the ampoule 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 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Diarrhea, nausea, abdominal pain, vomiting, loss of appetite, constipation, indigestion, bloating, weight loss, altered taste, flatulence, dry mouth
- Fatigue, weakness, discomfort, muscle and joint pain, drowsiness, fainting, dizziness, tremor
- Local pain, redness, irritation, itching, rash, hives and/or swelling at the injection site
- Dry, itchy, sweaty, bruised skin
- Headache
- Hair loss
- Blurred vision
- Flushing

If any of these affects you severely or does not go away, tell your doctor.

SIGNIFOR can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
High level of sugar in the blood excessive thirst, high urine output, increased appetite with weight loss, tiredness, nausea, vomiting, abdominal pain			√
Gallstones or complications - right-sided chest pain below rib cage -pain in the back right shoulder blade - nausea, vomiting, gas, burping - fever with chills, abdominal pain, or yellowing of skin/eye			√
Common			
Low cortisol levels extreme weakness, weight loss, nausea, vomiting, low blood pressure			√
Adrenal Insufficiency Fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain		√	
Heartbeat disturbance weakness, tiredness, shortness of breath, lightheadedness, fainting, dizziness, palpitations, seizures			√
Prolonged QT interval dizziness, palpitations, fainting, seizures			√
Low blood pressure Dizziness, fainting, lightheadedness		√	
High blood pressure headache	√		
Liver disorder nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine, abdominal pain			√
Pancreatic disorder acute or chronic abdominal pain (frequently radiating to the back), indigestion, nausea and vomiting, diarrhea, swollen and tender abdomen, bloating			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Coagulation disorder severe bruising or unusual bleeding from the skin or other areas			√
Uncommon			
Low level of red blood cells: tiredness, fatigue, pale skin			√
Reported from Post-Marketing with Unknown Frequency			
Increased ketones in urine or blood fruity scented breath, trouble breathing, confusion			√

This is not a complete list of side effects. For any unexpected effects while taking SIGNIFOR, contact your doctor or pharmacist.

HOW TO STORE IT

- Store between 15- 30°C.
- Keep this medicine out of the reach and sight of children.
- Store in the original package in order to protect from light.

Medicines should not be disposed via household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

If you want more information about SIGNIFOR:

- Talk to your healthcare professional
- This document plus the full product monograph, prepared for health professionals can be found at: www.recordatirarediseases.com/ca or by contacting the sponsor, Recordati Rare Diseases Canada Inc., at: 1-905-827-1300

[Pr] SIGNIFOR is a registered trademark

This leaflet was prepared by:
Recordati Rare Diseases Canada Inc.
Toronto, ON, M4N 3N1

Last revised: July 8, 2020