

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.3 mg solution for injection
Signifor 0.6 mg solution for injection
Signifor 0.9 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Signifor 0.3 mg solution for injection

One ampoule of 1 ml contains 0.3 mg pasireotide (as pasireotide diaspertate).

Signifor 0.6 mg solution for injection

One ampoule of 1 ml contains 0.6 mg pasireotide (as pasireotide diaspertate).

Signifor 0.9 mg solution for injection

One ampoule of 1 ml contains 0.9 mg pasireotide (as pasireotide diaspertate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended initial dose is 0.6 mg pasireotide by subcutaneous injection twice a day.

Two months after the start of Signifor therapy, patients should be evaluated for clinical benefit. Patients who experience a significant reduction in urinary free cortisol (UFC) levels should continue to receive Signifor for as long as benefit is derived. A dose increase to 0.9 mg may be considered based on the response to the treatment, as long as the 0.6 mg dose is well tolerated by the patient. Patients who have not responded to Signifor after two months of treatment should be considered for discontinuation.

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

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

Switch from intramuscular to subcutaneous formulation

There are no clinical data available on switching from the intramuscular to the subcutaneous

pasireotide formulation. If such a switch should be required, it is recommended to maintain an interval of at least 28 days between the last intramuscular injection and the first subcutaneous injection, and to initiate the subcutaneous injections at a dose of 0.6 mg pasireotide twice a day. The patient should be monitored for response and tolerability and further dose adjustments may be needed.

Special populations

Paediatric population

The safety and efficacy of Signifor in children and adolescents aged 0 to 18 years have not been established. No data are available.

Elderly patients (≥65 years)

Data on the use of Signifor in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment is required in these patients (see section 5.2).

Renal impairment

No dose adjustment is required in patients with impaired renal function (see section 5.2).

Hepatic impairment

Dose adjustment is not required in patients with mildly impaired hepatic function (Child Pugh A). The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 0.3 mg twice a day (see section 5.2). The maximum recommended dose for these patients is 0.6 mg twice a day. Signifor should not be used in patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 4.4).

Method of administration

Signifor is to be administered subcutaneously by self injection. Patients should receive instructions from the physician or a healthcare 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 or waistline).

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe hepatic impairment (Child Pugh C).

4.4 Special warnings and precautions for use

Glucose metabolism

Alterations in blood glucose levels have been frequently reported in healthy volunteers and patients treated with pasireotide. Hyperglycaemia and, less frequently, hypoglycaemia, were observed in subjects participating in clinical studies with pasireotide (see section 4.8).

The degree of hyperglycaemia appeared to be higher in patients with pre-diabetic conditions or established diabetes mellitus. During the pivotal study, HbA_{1c} levels increased significantly and stabilised but did not return to baseline values (see section 4.8). More cases of discontinuation and a higher reporting rate of severe adverse events due to hyperglycaemia were reported in patients treated with the dose of 0.9 mg twice daily.

The development of hyperglycaemia appears to be related to decreases in secretion of insulin

(particularly in the post-dose period) and of incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]).

Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done weekly for the first two to three months and periodically thereafter, as clinically appropriate, as well as over the first two to four weeks after any dose increase. In addition, monitoring of FPG 4 weeks and HbA_{1c} 3 months after the end of the treatment should be performed.

If hyperglycaemia develops in a patient being treated with Signifor, the initiation or adjustment of antidiabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycaemia. If uncontrolled hyperglycaemia persists despite appropriate medical management, the dose of Signifor should be reduced or Signifor treatment discontinued (see also section 4.5).

There have been post-marketing cases of ketoacidosis with Signifor in patients with and without a history of diabetes. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of diabetes history.

In patients with poor glycaemic control (as defined by HbA_{1c} values >8% while receiving anti-diabetic therapy), diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy.

Liver tests

Mild transient elevations in aminotransferases are commonly observed in patients treated with pasireotide. Rare cases of concurrent elevations in ALT (alanine aminotransferase) greater than 3 x ULN and bilirubin greater than 2 x ULN have also been observed (see section 4.8). Monitoring of liver function is recommended prior to treatment with pasireotide and after one, two, four, eight and twelve weeks during treatment. Thereafter liver function should be monitored as clinically indicated.

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be followed with frequent liver function monitoring until values return to pre-treatment levels. Therapy with pasireotide should be discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver dysfunction, in the event of a sustained increase in AST (aspartate aminotransferase) or ALT of 5 x ULN or greater, or if ALT or AST elevations greater than 3 x ULN occur concurrently with bilirubin elevations greater than 2 x ULN. Following discontinuation of treatment with pasireotide, patients should be monitored until resolution. Treatment should not be restarted.

Cardiovascular related events

Bradycardia has been reported with the use of pasireotide (see section 4.8). Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary (see also section 4.5).

Pasireotide has been shown to prolong the QT interval on the ECG in two dedicated healthy volunteer studies. The clinical significance of this prolongation is unknown.

In clinical studies in Cushing's disease patients, QTcF of >500 msec was observed in two out of 201 patients. These episodes were sporadic and of single occurrence with no clinical consequence observed. Episodes of torsade de pointes were not observed either in those studies or in clinical studies in other patient populations.

Pasireotide should be used with caution and the benefit risk carefully weighed in patients who are at significant risk of developing prolongation of QT, such as those:

- with congenital long QT syndrome.
- with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking antiarrhythmic medicinal products or other substances that are known to lead to QT prolongation (see section 4.5).
- with hypokalaemia and/or hypomagnesaemia.

Monitoring for an effect on the QTc interval is advisable and ECG should be performed prior to the start of Signifor therapy, one week after the beginning of the treatment and as clinically indicated thereafter. Hypokalaemia and/or hypomagnesaemia must be corrected prior to administration of Signifor and should be monitored periodically during therapy.

Hypocortisolism

Treatment with Signifor leads to rapid suppression of ACTH (adrenocorticotrophic hormone) secretion in Cushing's disease patients. Rapid, complete or near-complete suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially to transient hypocortisolism/hypoadrenalism.

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, hyperkalaemia, hyponatraemia, hypoglycaemia). In the event of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of Signifor therapy may be necessary.

Gallbladder and related events

Cholelithiasis (gallstones) is a recognised adverse reaction associated with long-term use of somatostatin analogues and has frequently been reported in clinical studies with pasireotide (see section 4.8). There have been post-marketing cases of cholangitis in patients taking Signifor, which in the majority of cases was reported as a complication of gallstones. Ultrasonic examination of the gallbladder before and at 6 to 12 month intervals during Signifor therapy is therefore recommended. The presence of gallstones in Signifor-treated patients is largely asymptomatic; symptomatic stones should be managed according to clinical practice.

Pituitary hormones

As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones other than ACTH cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T₄, GH/IGF-1) before and periodically during Signifor therapy should therefore be considered, as clinically appropriate.

Effect on female fertility

The therapeutic benefits of a reduction or normalisation of serum cortisol levels in female patients with Cushing's disease could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception during treatment with Signifor (see section 4.6).

Renal impairment

Due to the increase in unbound drug exposure, Signifor should be used with caution in patients with severe renal impairment or end stage renal disease (see section 5.2).

Sodium content

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Anticipated pharmacokinetic interactions resulting in effects on pasireotide

The influence of the P-gp inhibitor verapamil on the pharmacokinetics of subcutaneous pasireotide was tested in a drug-drug interaction study in healthy volunteers. No change in the pharmacokinetics (rate or extent of exposure) of pasireotide was observed.

Anticipated pharmacokinetic interactions resulting in effects on other medicinal products

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

Anticipated pharmacodynamic interactions

Medicinal products that prolong the QT interval

Pasireotide should be used with caution in patients who are concomitantly receiving medicinal products that prolong the QT interval, such as class Ia antiarrhythmics (e.g. quinidine, procainamide, disopyramide), class III antiarrhythmics (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide), certain antibacterials (intravenous erythromycin, pentamidine injection, clarithromycin, moxifloxacin), certain antipsychotics (e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone), certain antihistamines (e.g. terfenadine, astemizole, mizolastine), antimalarials (e.g. chloroquine, halofantrine, lumefantrine), certain antifungals (ketoconazole, except in shampoo) (see also section 4.4).

Bradycardic medicinal products

Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving pasireotide concomitantly with bradycardic medicinal products, such as beta blockers (e.g. metoprolol, carteolol, propranolol, sotalol), acetylcholinesterase inhibitors (e.g. rivastigmine, physostigmine), certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil), certain antiarrhythmics (see also section 4.4).

Insulin and antidiabetic medicinal products

Dose adjustments (decrease or increase) of insulin and antidiabetic medicinal products (e.g. metformin, liraglutide, vildagliptin, nateglinide) may be required when administered concomitantly with pasireotide (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of pasireotide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Pasireotide is not recommended for use during pregnancy and in women of childbearing potential who are not using contraception (see section 4.4).

Breast-feeding

It is unknown whether pasireotide is excreted in human milk. Available data in rats have shown excretion of pasireotide in milk (see section 5.3). Breast-feeding should be discontinued during treatment with Signifor.

Fertility

Studies in rats have shown effects on female reproductive parameters (see section 5.3). The clinical relevance of these effects in humans is unknown.

4.7 Effects on ability to drive and use machines

Signifor may have a minor 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, dizziness or headache during treatment with Signifor.

4.8 Undesirable effects

Summary of the safety profile

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

The data described below reflect exposure of 162 Cushing's disease patients to Signifor in the phase III study. At study entry patients were randomised to receive twice-daily doses of either 0.6 mg or 0.9 mg Signifor. The mean age of patients was approximately 40 years and the majority of patients (77.8%) were female. Most (83.3%) patients had persistent or recurrent Cushing's disease and few ($\leq 5\%$) in either treatment group had received previous pituitary irradiation. The median exposure to the treatment up to the cut-off date of the primary efficacy and safety analysis was 10.37 months (0.03-37.8), with 66.0% of patients having at least six months' exposure.

Grade 1 and 2 adverse reactions were reported in 57.4% of patients. Grade 3 adverse reactions were observed in 35.8% of patients and Grade 4 adverse reactions in 2.5% of patients. Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia. The most common adverse reactions (incidence $\geq 10\%$) were diarrhoea, nausea, abdominal pain, cholelithiasis, injection site reactions, hyperglycaemia, diabetes mellitus, fatigue and glycosylated haemoglobin increased.

Tabulated list of adverse reactions

Adverse reactions reported up to the cut-off date of the analysis are presented in Table 1. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies were defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); not known (cannot be estimated from the available data).

Table 1 Adverse reactions in the phase III study and from post-marketing experience in Cushing's disease patients

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders			Anaemia	
Endocrine disorders		Adrenal insufficiency		
Metabolism and nutrition disorders	Hyperglycaemia, diabetes mellitus	Decreased appetite, type 2 diabetes mellitus, glucose tolerance impaired		Diabetic ketoacidosis
Nervous system disorders		Headache, dizziness		
Cardiac disorders		Sinus bradycardia, QT prolongation		
Vascular disorders		Hypotension		
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea	Vomiting, abdominal pain upper		
Hepatobiliary disorders	Cholelithiasis	Cholecystitis *, cholestasis		
Skin and subcutaneous tissue disorders		Alopecia, pruritus		
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia		
General disorders and administration site conditions	Injection site reaction, fatigue			
Investigations	Glycosylated haemoglobin increased	Gamma glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, blood glucose increased, blood amylase increased, prothrombin time prolonged		
* Cholecystitis includes cholecystitis acute				

Description of selected adverse reactions

Glucose metabolism disorders

Elevated glucose was the most frequently reported Grade 3 laboratory abnormality (23.2% of patients) in the phase III study in Cushing's disease patients. Mean HbA_{1c} increases were less pronounced in patients with normal glycaemia (n=62 overall) at study entry (i.e. 5.29% and 5.22% at baseline and 6.50% and 6.75% at month 6 for the 0.6 and 0.9 mg twice daily dose groups, respectively) relative to pre-diabetic patients (i.e. n=38 overall; 5.77% and 5.71% at baseline and 7.45% and 7.13% at month 6) or diabetic patients (i.e. n=54 overall; 6.50% and 6.42% at baseline and 7.95% and 8.30% at month 6). Mean fasting plasma glucose levels commonly increased within the first month of treatment, with decreases and stabilisation observed in subsequent months. Fasting plasma glucose and HbA_{1c} values generally decreased over the 28 days following pasireotide discontinuation but remained above baseline values. Long-term follow-up data are not available. Patients with baseline HbA_{1c} ≥7% or who were taking antidiabetic medicinal products prior to randomisation tended to have higher mean changes in fasting plasma glucose and HbA_{1c} relative to other patients. Adverse reactions of hyperglycaemia and diabetes mellitus led to study discontinuation in 5 (3.1%) and 4 (2.5%) patients, respectively. One case of ketosis and one case of ketoacidosis have been reported during compassionate use of Signifor.

Monitoring of blood glucose levels in patients treated with Signifor is recommended (see section 4.4).

Gastrointestinal disorders

Gastrointestinal disorders were frequently reported with Signifor. These reactions were usually of low grade, required no intervention and improved with continued treatment.

Injection site reactions

Injection site reactions were reported in 13.6% of patients enrolled in the phase III study in Cushing's disease. Injection site reactions were also reported in clinical studies in other populations. The reactions were most frequently reported as local pain, erythema, haematoma, haemorrhage and pruritus. These reactions resolved spontaneously and required no intervention.

Liver enzymes

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

Monitoring of liver enzymes is recommended before and during treatment with Signifor (see section 4.4), as clinically appropriate.

Pancreatic enzymes

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Doses up to 2.1 mg twice a day have been used in healthy volunteers, with the adverse reaction diarrhoea being observed at a high frequency.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatostatin and analogues, ATC code: H01CB05

Mechanism of action

Pasireotide is a novel cyclohexapeptide, injectable somatostatin analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somatotropin release inhibiting factor [SRIF]) and other somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors. Five human somatostatin receptor subtypes are known: *hsst1*, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogues bind to *hsst* receptors with different potencies (see Table 2). Pasireotide binds with high affinity to four of the five *hssts*.

Table 2 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and lanreotide to the five human somatostatin receptor subtypes (*hsst1-5*)

Compound	<i>hsst1</i>	<i>hsst2</i>	<i>hsst3</i>	<i>hsst4</i>	<i>hsst5</i>
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	>1,000	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	>1,000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

Results are the mean±SEM of IC₅₀ values expressed as nmol/l.

Pharmacodynamic effects

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumours in which hormones are excessively secreted, including ACTH in Cushing's disease.

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

Clinical efficacy and safety

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

The study enrolled 162 patients with a baseline UFC >1.5 x ULN who were randomised in a 1:1 ratio to receive a subcutaneous dose of either 0.6 mg or 0.9 mg Signifor twice daily. After three months of

treatment, patients with a mean 24-hour UFC $\leq 2 \times$ ULN and below or equal to their baseline value continued blinded treatment at the randomised dose until month 6. Patients who did not meet these criteria were unblinded and the dose was increased by 0.3 mg twice daily. After the initial 6 months in the study, patients entered an additional 6-month open-label treatment period. If response was not achieved at month 6 or if the response was not maintained during the open-label treatment period, dosage could be increased by 0.3 mg twice daily. The dose could be reduced by decrements of 0.3 mg twice daily at any time during the study for reasons of intolerability.

The primary efficacy end-point was the proportion of patients in each arm who achieved normalisation of mean 24-hour UFC levels (UFC \leq ULN) after 6 months of treatment and who did not have a dose increase (relative to randomised dose) during this period. Secondary end-points included, among others, changes from baseline in: 24-hour UFC, plasma ACTH, serum cortisol levels, and clinical signs and symptoms of Cushing's disease. All analyses were conducted based on the randomised dose groups.

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

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

Results

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

A supportive efficacy analysis was conducted in which patients were further classified into 3 response categories regardless of up-titration at month 3: Fully controlled (UFC $\leq 1.0 \times$ ULN), partially controlled (UFC $> 1.0 \times$ ULN but with a reduction in UFC $\geq 50\%$ compared to baseline) or uncontrolled (reduction in UFC $< 50\%$). The total proportion of patients with either full or partial mean UFC control at month 6 was 34% and 41% of the randomised patients to the 0.6 mg and 0.9 mg dose, respectively. Patients uncontrolled at both month 1 and month 2 are likely (90%) to remain uncontrolled at months 6 and 12.

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

Decreases were also demonstrated by the overall percentage of change in mean and median UFC levels at month 6 and 12 as compared to baseline values (see Table 3). Reductions in plasma ACTH levels were also observed at each time point for each dose group.

Table 3 Percentage change in mean and median UFC levels per randomised dose group at

month 6 and month 12 compared to baseline values

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

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

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Signifor in all subsets of the paediatric population in pituitary-dependant Cushing's disease, overproduction of pituitary ACTH and pituitary dependant hyperadrenocorticism (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

In healthy volunteers, pasireotide is widely distributed with large apparent volume of distribution ($V_z/F > 100$ litres). Distribution between blood cells 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.

Based on *in vitro* data pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein). Based on *in vitro* data pasireotide is not a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1), OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1. At therapeutic dose levels pasireotide is also not an inhibitor of UGT1A1, OATP, 1B1 or 1B3, P-gp, BCRP, MRP2 and BSEP.

Biotransformation

Pasireotide is metabolically highly stable and *in vitro* data show that pasireotide is not a substrate, inhibitor or inducer of any major enzymes of CYP450. In healthy volunteers, pasireotide is predominantly found in unchanged form in plasma, urine and faeces.

Elimination

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion), with a small contribution of the renal route. In a human ADME study 55.9±6.63% of the radioactive dose was recovered over the

first 10 days after administration, including $48.3 \pm 8.16\%$ of the radioactivity in faeces and $7.63 \pm 2.03\%$ 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.

Linearity and time dependency

In Cushing's disease patients, pasireotide demonstrates linear and time-independent pharmacokinetics in the dose range of 0.3 mg to 1.2 mg twice a day. Population pharmacokinetic analysis suggests that based on C_{max} and AUC, 90% of steady state in Cushing's disease patients is reached after approximately 1.5 and 15 days, respectively.

Special populations

Paediatric population

No studies have been performed in paediatric patients.

Patients with renal impairment

Renal clearance has a minor contribution to the elimination of pasireotide in humans. In a clinical study with single subcutaneous dose administration of 900 μ g pasireotide in subjects with impaired renal function, renal impairment of mild, moderate or severe degree, or end stage renal disease (ESRD) did not have a significant impact on total pasireotide plasma exposure. The unbound plasma pasireotide exposure ($AUC_{inf,u}$) was increased in subjects with renal impairment (mild: 33%; moderate: 25%, severe: 99%, ESRD: 143%) compared to control subjects.

Patients with hepatic impairment

In a clinical study in subjects with impaired hepatic function (Child-Pugh A, B and C), statistically significant differences were found in subjects with moderate and severe hepatic impairment (Child-Pugh B and C). In subjects with moderate and severe hepatic impairment, AUC_{inf} was increased 60% and 79%, C_{max} was increased 67% and 69%, and CL/F was decreased 37% and 44%, respectively.

Elderly patients (≥ 65 years)

Age has been found to be a covariate in the population pharmacokinetic analysis of Cushing's disease patients. Decreased total body clearance and increased pharmacokinetic exposures have been seen with increasing age. In the studied age range 18-73 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.

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.

Demographics

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

Body weight has been found to be a covariate in the population pharmacokinetic analysis of Cushing's disease patients. For a range of 60-100 kg the reduction in AUC_{ss} with increasing weight is predicted to be approximately 27%, which is considered moderate and of minor clinical significance.

5.3 Preclinical safety data

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction

and development. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Pasireotide was not genotoxic in *in vitro* and *in vivo* assays.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Tartaric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

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

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

Packs containing 6 ampoules or multipacks containing 18 (3 x 6), 30 (5 x 6) or 60 (10 x 6) ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Signifor solution for injection should be free of visible particles, clear and colourless. Do not use Signifor if the solution is not clear or contains particles.

For information on the instructions for use, please see the end of the package leaflet “How to inject Signifor”.

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

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

Signifor 0.3 mg solution for injection
EU/1/12/753/001-004

Signifor 0.6 mg solution for injection
EU/1/12/753/005-008

Signifor 0.9 mg solution for injection
EU/1/12/753/009-0012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2012
Date of latest renewal: 18 November 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Signifor 10 mg powder and solvent for suspension for injection
Signifor 20 mg powder and solvent for suspension for injection
Signifor 30 mg powder and solvent for suspension for injection
Signifor 40 mg powder and solvent for suspension for injection
Signifor 60 mg powder and solvent for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Signifor 10 mg powder and solvent for suspension for injection
One vial contains 10 mg pasireotide (as pasireotide pamoate).

Signifor 20 mg powder and solvent for suspension for injection
One vial contains 20 mg pasireotide (as pasireotide pamoate).

Signifor 30 mg powder and solvent for suspension for injection
One vial contains 30 mg pasireotide (as pasireotide pamoate).

Signifor 40 mg powder and solvent for suspension for injection
One vial contains 40 mg pasireotide (as pasireotide pamoate).

Signifor 60 mg powder and solvent for suspension for injection
One vial contains 60 mg pasireotide (as pasireotide pamoate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection (powder for injection).

Powder: slightly yellowish to yellowish powder.

Solvent: clear, colourless to slightly yellow or slightly brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.

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

The 60 mg strength is only to be used in the treatment of acromegaly.

4.2 Posology and method of administration

Posology

Acromegaly

The recommended initial dose for the treatment of acromegaly is 40 mg of pasireotide every 4 weeks.

The dose may be increased to a maximum of 60 mg for patients whose growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) levels are not fully controlled after 3 months of treatment with Signifor at 40 mg.

Management of suspected adverse reactions or over-response to treatment (IGF-1 < lower limit of normal) may require temporary dose reduction of Signifor. The dose may be decreased either temporarily or permanently.

Cushing's disease

The recommended initial dose for the treatment of Cushing's disease is 10 mg of pasireotide by deep intramuscular injection every 4 weeks.

The patient should be evaluated for clinical benefit after the first month of treatment and periodically thereafter. The dose may be titrated every 2 to 4 months based on response and tolerability. The maximum dose of Signifor in Cushing's disease is 40 mg every 4 weeks. If no clinical benefit is observed, the patient should be considered for discontinuation.

Management of suspected adverse reactions or over-response to treatment (cortisol levels < lower limit of normal) may require dose reduction, interruption or discontinuation of Signifor.

Switch from subcutaneous to intramuscular formulation in Cushing's disease

There are no clinical data available on switching from the subcutaneous to the intramuscular pasireotide formulation. If such a switch should be required, the recommended initial dose for the treatment of Cushing's disease is 10 mg of pasireotide by deep intramuscular injection every 4 weeks. The patient should be monitored for response and tolerability and further dose adjustments may be needed.

Missed dose

If a dose of Signifor is missed the missed injection should be administered as soon as possible. The next dose should then be planned for 4 weeks after the injection is administered in order to resume the normal schedule of one dose every 4 weeks.

Special populations

Elderly patients (≥65 years)

Data on the use of Signifor in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment is required in these patients (see section 5.2).

Renal impairment

No dose adjustment is required in patients with impaired renal function (see section 5.2).

Hepatic impairment

Dose adjustment is not required in patients with mildly impaired hepatic function (Child Pugh A).

Acromegaly: the recommended initial dose for acromegaly patients with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks, and the maximum recommended dose for these patients is 40 mg every 4 weeks (see section 5.2).

Cushings disease: the recommended initial dose for Cushing's disease patients with moderate hepatic impairment (Child Pugh B) is 10 mg every 4 weeks, and the maximum recommended dose for these patients is 20 mg every 4 weeks (see section 5.2).

Signifor should not be used in patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 4.4).

Paediatric population

The safety and efficacy of Signifor in children and adolescents aged 0 to 18 years have not been

established. No data are available.

Method of administration

Signifor is to be administered by deep intramuscular injection by a trained healthcare professional. Signifor suspension must only be prepared immediately before administration.

The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe hepatic impairment (Child Pugh C).

4.4 Special warnings and precautions for use

Glucose metabolism

Alterations in blood glucose levels have been frequently reported in healthy volunteers and patients treated with pasireotide. Hyperglycaemia and, less frequently, hypoglycaemia, were observed in subjects participating in clinical studies with pasireotide (see section 4.8).

In patients who developed hyperglycaemia, the condition generally appeared to respond to antidiabetic therapy. Dose reductions or discontinuation of treatment with pasireotide due to hyperglycaemia were infrequent in clinical studies with pasireotide.

The development of hyperglycaemia appears to be related to decreases in secretion of insulin and of incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulintropic polypeptide [GIP]).

Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done weekly for the first three months and periodically thereafter, as clinically appropriate, as well as over the first four to six weeks after any dose increase. In addition, monitoring of FPG 4 weeks and HbA_{1c} 3 months after the end of the treatment should be performed.

If hyperglycaemia develops in a patient being treated with Signifor, the initiation or adjustment of antidiabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycaemia. If uncontrolled hyperglycaemia persists despite appropriate medical management, the dose of Signifor should be reduced or Signifor treatment discontinued (see also section 4.5).

There have been post-marketing cases of ketoacidosis with Signifor in patients with and without a history of diabetes. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of diabetes history.

In patients with poor glycaemic control (as defined by HbA_{1c} values >8% while receiving anti-diabetic therapy), diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy.

Liver tests

Mild transient elevations in aminotransferases are commonly observed in patients treated with pasireotide. Rare cases of concurrent elevations in ALT (alanine aminotransferase) greater than 3 x ULN and bilirubin greater than 2 x ULN have also been observed (see section 4.8). Monitoring of liver function is recommended prior to treatment with pasireotide intramuscular use and after the first two to three weeks, then monthly for three months on treatment. Thereafter liver function should be monitored as clinically indicated.

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

Cardiovascular related events

Bradycardia has been reported with the use of pasireotide (see section 4.8). Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary (see also section 4.5).

Pasireotide has been shown to prolong the QT interval on the ECG in two dedicated healthy volunteer studies performed with the subcutaneous formulation. The clinical significance of this prolongation is unknown. The phase III clinical studies in acromegaly patients did not identify any clinically meaningful differences in the QT prolongation events between pasireotide intramuscular use and the somatostatin analogues which were tested as active comparator. All QT-related events were transient and resolved without therapeutic intervention.

Episodes of torsade de pointes were not observed in any clinical study with pasireotide.

Pasireotide should be used with caution and the benefit risk carefully weighed in patients who are at significant risk of developing prolongation of QT, such as those:

- with congenital long QT syndrome.
- with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking antiarrhythmic medicinal products or other substances that are known to lead to QT prolongation (see section 4.5).
- with hypokalaemia and/or hypomagnesaemia.

A baseline ECG is recommended prior to initiating therapy with Signifor. Monitoring for an effect on the QTc interval is advisable 21 days after the beginning of the treatment and as clinically indicated thereafter. Hypokalaemia and/or hypomagnesaemia must be corrected prior to administration of Signifor and should be monitored periodically during therapy.

Hypocortisolism

The suppression of ACTH (adrenocorticotrophic hormone) secretion can result in hypocortisolism in patients treated with Signifor. 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, hyperkalaemia, hyponatraemia, hypoglycaemia). In the event of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose

reduction or interruption of Signifor therapy may be necessary. Rapid decreases in cortisol levels may be associated with decreases in white blood cell count.

Gallbladder and related events

Cholelithiasis (gallstones) is a recognised adverse reaction associated with somatostatin analogues and has frequently been reported in clinical studies with pasireotide (see section 4.8). There have been post-marketing cases of cholangitis in patients taking Signifor, which in the majority of cases was reported as a complication of gallstones. Ultrasonic examination of the gallbladder before and at 6 to 12 month intervals during Signifor therapy is therefore recommended. The presence of gallstones in Signifor-treated patients is largely asymptomatic; symptomatic stones should be managed according to clinical practice.

Pituitary hormones

As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones other than GH and/or IGF-1 in patients with acromegaly and ACTH/cortisol in patients with Cushing's disease cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T₄) before and periodically during Signifor therapy should therefore be considered, as clinically appropriate.

Effect on female fertility

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalisation of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients and of a reduction or normalisation of serum cortisol levels in female patients with Cushing's disease could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with Signifor (see section 4.6).

Coagulation abnormalities

Patients with significantly increased prothrombin time (PT) and partial thromboplastin time (PTT) values or patients receiving coumarin-derivative or heparin-derivative anticoagulants were excluded from clinical studies with pasireotide as the safety of the combination with such anticoagulants has not been established. If concomitant use of coumarin-derivative or heparin-derivative anticoagulants with Signifor intramuscular use cannot be avoided, patients should be monitored regularly for alterations in their coagulation parameters (PT and PTT) and the anticoagulant dose adjusted accordingly.

Renal impairment

Due to the increase in unbound drug exposure, Signifor should be used with caution in patients with severe renal impairment or end stage renal disease (see section 5.2).

Sodium content

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Anticipated pharmacokinetic interactions resulting in effects on pasireotide

The influence of the P-gp inhibitor verapamil on the pharmacokinetics of subcutaneous pasireotide was tested in a drug-drug interaction study in healthy volunteers. No change in the pharmacokinetics (rate or extent of exposure) of pasireotide was observed.

Anticipated pharmacokinetic interactions resulting in effects on other medicinal products

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

Anticipated pharmacodynamic interactions

Medicinal products that prolong the QT interval

Pasireotide should be used with caution in patients who are concomitantly receiving medicinal products that prolong the QT interval, such as class Ia antiarrhythmics (e.g. quinidine, procainamide, disopyramide), class III antiarrhythmics (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide), certain antibacterials (intravenous erythromycin, pentamidine injection, clarithromycin, moxifloxacin), certain antipsychotics (e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone), certain antihistamines (e.g. terfenadine, astemizole, mizolastine), antimalarials (e.g. chloroquine, halofantrine, lumefantrine), certain antifungals (ketoconazole, except in shampoo) (see also section 4.4).

Bradycardic medicinal products

Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving pasireotide concomitantly with bradycardic medicinal products, such as beta blockers (e.g. metoprolol, carteolol, propranolol, sotalol), acetylcholinesterase inhibitors (e.g. rivastigmine, physostigmine), certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil), certain antiarrhythmics (see also section 4.4).

Insulin and antidiabetic medicinal products

Dose adjustments (decrease or increase) of insulin and antidiabetic medicinal products (e.g. metformin, liraglutide, vildagliptin, nateglinide) may be required when administered concomitantly with pasireotide (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of pasireotide in pregnant women. Studies in animals in which pasireotide was administered via the subcutaneous route have shown reproductive toxicity (see section 5.3). Pasireotide is not recommended for use during pregnancy and in women of childbearing potential who are not using contraception (see section 4.4).

Breast-feeding

It is unknown whether pasireotide is excreted in human milk. Available data in rats in which pasireotide was administered via the subcutaneous route have shown excretion of pasireotide in milk (see section 5.3). Breast-feeding should be discontinued during treatment with Signifor.

Fertility

Studies in rats in which pasireotide was administered via the subcutaneous route have shown effects on female reproductive parameters (see section 5.3). The clinical relevance of these effects in humans is unknown.

4.7 Effects on ability to drive and use machines

Signifor may have a minor 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, dizziness or headache during treatment with Signifor.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of pasireotide intramuscular use is consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use. The safety profile of pasireotide intramuscular use was largely similar between the acromegaly and Cushing's disease indications.

Acromegaly

In acromegaly, the safety assessment was made based on 491 patients who received pasireotide (419 patients received pasireotide intramuscular use and 72 received pasireotide subcutaneous use) in phase I, II and III studies. The most common adverse reactions (incidence $\geq 1/10$) from the pooled safety data from the phase III studies C2305 and C2402 were (in decreasing order): diarrhoea (most common in study C2305), cholelithiasis, hyperglycaemia (most common in study C2402) and diabetes mellitus. Common Toxicity Criteria (CTC) Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia.

Cushing's disease

In Cushing's disease, the safety assessment of the intramuscular formulation was made based on 150 patients who received pasireotide in the phase III study G2304 (median duration of exposure: 57 weeks). Patients were randomised in a 1:1 ratio to receive starting doses of either 10 mg or 30 mg pasireotide, with a possibility to up-titrate to a maximum dose of 40 mg every 28 days. The most common adverse reactions (incidence $\geq 1/10$) in the phase III study G2304 were hyperglycaemia, diarrhoea, cholelithiasis and diabetes mellitus. The frequency and severity of adverse reactions tended to be higher with the higher starting dose of 30 mg, but this was not consistent for all adverse reactions.

Tabulated list of adverse reactions

The adverse reactions in Table 1 include events reported in the pivotal studies with the intramuscular formulation in patients with acromegaly and with Cushing's disease. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies were defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); not known (cannot be estimated from the available data).

Table 1 Adverse reactions by preferred term for pasireotide intramuscular use

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders		Anaemia		
Endocrine disorders		Adrenal insufficiency*		
Metabolism and nutrition disorders	Hyperglycaemia, diabetes mellitus	Type 2 diabetes mellitus, glucose tolerance impaired, decreased appetite		Diabetic ketoacidosis
Nervous system disorders		Headache, dizziness		
Cardiac disorders		Sinus bradycardia*, QT prolongation		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain*	Abdominal distension, vomiting		
Hepatobiliary disorders	Cholelithiasis	Cholecystitis*, cholestasis		
Skin and subcutaneous tissue disorders		Alopecia, pruritus		
General disorders and administration site conditions	Fatigue*	Injection site reaction*		
Investigations		Glycosylated haemoglobin increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood glucose increased, blood creatine phosphokinase increased, lipase increased	Amylase increased, prothrombin time prolonged	
* Grouped terms: Adrenal insufficiency includes adrenal insufficiency and blood cortisol decreased. Sinus bradycardia includes bradycardia and sinus bradycardia. Abdominal pain includes abdominal pain and abdominal pain upper. Injection site reaction includes injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction, injection site hypersensitivity and injection site swelling. Cholecystitis includes cholecystitis acute and cholecystitis chronic. Fatigue includes fatigue and asthenia.				

Description of selected adverse reactions

Glucose metabolism disorders

Acromegaly

In acromegaly patients elevated fasting glucose level was the most frequently reported grade 3/4 laboratory abnormality in the two phase III studies. In study C2305, grade 3 elevated fasting glucose levels were reported in 9.7% and 0.6% and grade 4 in 0.6% and 0% of acromegaly patients treated with pasireotide intramuscular use and octreotide intramuscular use, respectively. In study C2402, grade 3 elevated fasting glucose levels were reported in 14.3% and 17.7% of acromegaly patients treated with pasireotide intramuscular use 40 mg and 60 mg respectively, and in no patients in the active control group. Two cases of hyperglycaemia-related emergencies (diabetic ketoacidosis and diabetic hyperglycaemic coma) were reported following a dose increase of pasireotide to 60 mg in medical treatment naïve patients; one in a patient with untreated hyperglycaemia and HbA_{1c} >8% prior to initiation of pasireotide and the other in a patient with untreated hyperglycaemia and a fasting plasma glucose of 359 mg/dl, respectively. In both studies, mean FPG and HbA_{1c} levels peaked within the first three months of treatment with pasireotide intramuscular use. In medically naïve patients (study C2305), the mean absolute increase in FPG and HbA_{1c} was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

The degree and frequency of hyperglycaemia observed in the two pivotal studies in acromegaly patients were higher with Signifor intramuscular use than with active control (octreotide intramuscular use or lanreotide deep subcutaneous injection). In a pooled analysis of the two pivotal studies, the overall incidence of hyperglycaemia-related adverse reactions was 58.6% (all grades) and 9.9% (CTC Grade 3 and 4) for Signifor intramuscular use versus 18.0% (all grades) and 1.1% (CTC Grade 3 and 4) for the active control. In the pivotal study with patients inadequately controlled on another somatostatin analogue, the proportion of patients not previously treated with anti-diabetic agents who required commencement of anti-diabetic therapy during the study was 17.5% and 16.1% in the Signifor 40 mg and 60 mg arms compared to 1.5% in the active control arm. In the pivotal study with patients who did not receive prior medical treatment, the proportion of patients who required commencement of anti-diabetic therapy during the study was 36% in the Signifor arm compared to 4.4% in the active control arm.

Cushing's disease

In Cushing's disease patients, elevated FPG levels was the most frequently reported CTC Grade 3 laboratory abnormality (14.7% of patients) in the phase III study G2304; with no cases of Grade 4 reported. Mean HbA_{1c} increases were less pronounced in patients with normal glycaemia at study entry in comparison to pre-diabetic patients or diabetic patients. Mean FPG levels commonly increased within the first month of treatment with decreases and stabilisation observed in subsequent months. FPG and HbA_{1c} increases were dose-dependent, and values generally decreased following pasireotide intramuscular use discontinuation but remained above baseline values. The overall incidence of hyperglycaemia-related adverse reactions was 75.3% (all grades) and 22.7% (CTC Grade 3). Adverse reactions of hyperglycaemia and diabetes mellitus led to study discontinuation in 3 (2.0%) and 4 patients (2.7%), respectively.

The elevations of fasting plasma glucose and HbA_{1c} observed with pasireotide intramuscular use treatment are reversible after discontinuation.

Monitoring of blood glucose levels in patients treated with Signifor is recommended (see section 4.4).

Gastrointestinal disorders

Gastrointestinal disorders were frequently reported with Signifor. These reactions were usually of low grade, required no intervention and improved with continued treatment. In acromegaly patients, gastrointestinal disorders were less frequent in inadequately controlled patients compared to medically naïve patients.

Injection site reactions

In the phase III studies, injection site related reactions (e.g. injection site pain, injection site

discomfort) were mostly grade 1 or 2 in severity. The incidence of such events was highest in the first 3 months of treatment. In the acromegaly studies, the events were comparable between pasireotide intramuscular use and octreotide intramuscular use treated patients, and were less frequent in inadequately controlled patients compared to medically naïve patients.

QT prolongation

In the acromegaly study C2305, the proportion of patients with newly occurring notable QT/QTc intervals was comparable between pasireotide intramuscular use and octreotide intramuscular use groups up to crossover, with few notable outlying values. QTcF >480 ms was reported for 3 versus 2 patients in the pasireotide intramuscular use and octreotide intramuscular use groups, respectively, and QTcF >60 ms prolonged from baseline was reported for 2 versus 1 patients in the respective groups. In study C2402, the only notable outlier was a QTcF value >480 ms in 1 patient in the pasireotide intramuscular use 40 mg group. In the Cushing's disease study G2304, a QTcF value >480 ms was reported for 2 patients. No QTcF values >500 ms were observed in any of the pivotal studies.

Liver enzymes

Transient elevations in liver enzymes have been reported with the use of somatostatin analogues and were also observed in healthy subjects and patients receiving pasireotide in clinical studies. The elevations were mostly asymptomatic, of low grade and reversible with continued treatment. A few cases of concurrent elevations in ALT greater than 3 x ULN and bilirubin greater than 2 x ULN have been observed with the subcutaneous formulation, however not in patients treated with pasireotide intramuscular use. All observed cases of concurrent elevations were identified within ten days of initiation of treatment. The patients recovered without clinical sequelae and liver function test results returned to baseline values after discontinuation of treatment.

Monitoring of liver enzymes is recommended before and during treatment with Signifor (see section 4.4), as clinically appropriate.

Pancreatic enzymes

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatostatin and analogues, ATC code: H01CB05

Mechanism of action

Pasireotide is a cyclohexapeptide, injectable somatostatin analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somatotropin release inhibiting factor [SRIF]) and other somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors. Five human somatostatin receptor subtypes are known: *hsst1*, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogues bind to *hsst* receptors with different potencies (see Table 2). Pasireotide binds with high affinity to four of the five *hssts*.

Table 2 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and lanreotide to the five human somatostatin receptor subtypes (*hsst1-5*)

Compound	<i>hsst1</i>	<i>hsst2</i>	<i>hsst3</i>	<i>hsst4</i>	<i>hsst5</i>
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	>1,000	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	>1,000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

Results are the mean±SEM of IC₅₀ values expressed as nmol/l.

Pharmacodynamic effects

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumours in which hormones are excessively secreted, including GH in acromegaly and ACTH in Cushing's disease.

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

Due to its broad binding profile to somatostatin receptors, pasireotide has the potential to stimulate both *hsst2* and *hsst5* subtype receptors relevant for inhibition of GH and IGF-1 secretion and therefore to be effective for the treatment of acromegaly.

Glucose metabolism

In a randomised double-blinded mechanism study conducted in healthy volunteers, the development of hyperglycaemia with pasireotide administered as pasireotide subcutaneous use at doses of 0.6 and 0.9 mg twice a day was related to significant decreases in insulin secretion as well as incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulintropic polypeptide [GIP]). Pasireotide did not affect insulin sensitivity.

Clinical efficacy and safety

The efficacy of pasireotide intramuscular use has been demonstrated in two phase III, multicentre studies in acromegaly patients and in one phase III, multicentre study in Cushing's disease patients.

Acromegaly study C2402, inadequately controlled patients

Study C2402 was a phase III, multicentre, randomised, parallel-group, three-arm study of double-blind pasireotide intramuscular use 40 mg and 60 mg versus open-label octreotide intramuscular use 30 mg or lanreotide deep subcutaneous injection 120 mg in patients with inadequately controlled acromegaly. A total of 198 patients were randomised to receive pasireotide intramuscular use 40 mg (n=65), pasireotide intramuscular use 60 mg (n=65) or active control (n=68). 192 patients were treated. A total of 181 patients completed the core phase (24 weeks) of the study.

Inadequately controlled patients in study C2402 are defined as patients with a mean GH concentration

of a 5-point profile over a 2-hour period $>2.5 \mu\text{g/l}$ and sex- and age-adjusted IGF-1 $>1.3 \times \text{ULN}$. Patients had to be treated with maximum indicated doses of octreotide intramuscular use (30 mg) or lanreotide deep subcutaneous injection (120 mg) for at least 6 months prior to randomisation. Three-quarters of patients had previously been treated with octreotide intramuscular use and a quarter with lanreotide deep subcutaneous injection. Nearly half of the patients had additional prior medical treatment for acromegaly other than somatostatin analogues. Two-thirds of all patients had undergone prior surgery. Baseline mean GH was $17.6 \mu\text{g/l}$, $12.1 \mu\text{g/l}$ and $9.5 \mu\text{g/l}$, in the 40 mg, 60 mg and active control groups, respectively. IGF-1 mean values at baseline were 2.6, 2.8 and $2.9 \times \text{ULN}$, respectively.

The primary efficacy endpoint was to compare the proportion of patients achieving biochemical control (defined as mean GH levels $<2.5 \mu\text{g/l}$ and normalisation of sex- and age-adjusted IGF-1) at week 24 with pasireotide intramuscular use 40 mg or 60 mg versus continued treatment with active control (octreotide intramuscular use 30 mg or lanreotide deep subcutaneous injection 120 mg), separately. The study met its primary efficacy endpoint for both pasireotide intramuscular use doses. The proportion of patients achieving biochemical control was 15.4% (p-value = 0.0006) and 20.0% (p-value <0.0001) for pasireotide intramuscular use 40 mg and 60 mg, respectively at 24 weeks compared with zero in the active control arm (Table 3).

Table 3 Key results at week 24 (Study C2402)

	Signifor intramuscular use 40 mg N=65 n (%), p value	Signifor intramuscular use 60 mg N=65 n (%), p value	Active control N=68 n (%)
GH $<2.5 \mu\text{g/l}$ and normalised IGF-1*	10 (15.4%), p=0.0006	13 (20.0%), p <0.0001	0 (0%)
Normalisation of IGF-1	16 (24.6%), p <0.0001	17 (26.2%), p <0.0001	0 (0%)
GH $<2.5 \mu\text{g/l}$	23 (35.4%)	28 (43.1%)	9 (13.2%)

* Primary endpoint (patients with IGF-1 $<$ lower limit of normal (LLN) were not considered “responders”).

In patients treated with pasireotide intramuscular use in whom reductions in GH and IGF-1 levels were observed, these changes occurred during the first 3 months of treatment and were maintained up to week 24.

The proportion of patients with a reduction or no change in pituitary tumour volume at week 24 was 81.0% and 70.3% on pasireotide intramuscular use 40 and 60 mg, and 50.0% on active control. Furthermore, a higher proportion of patients on pasireotide intramuscular use (18.5% and 10.8% for 40 mg and 60 mg, respectively) than active comparator (1.5%) achieved a reduction in tumour volume of at least 25%.

Health-related quality of life measured by AcroQoL indicated statistically significant improvements from baseline to week 24 in the Physical, Psychological-Appearance and Global scores for the 60 mg group and the Physical sub-score for the 40mg group. Changes for the octreotide intramuscular use or lanreotide deep subcutaneous injection group were not statistically significant. The improvement observed up to week 24 between the treatment groups was also not statistically significant.

Acromegaly study C2305 patients who had no prior medical treatment

A phase III multicentre, randomised, blinded study was conducted to assess the safety and efficacy of pasireotide intramuscular use versus octreotide intramuscular use in medically naïve patients with active acromegaly. A total of 358 patients were randomised and treated. Patients were randomised in a 1:1 ratio to one of two treatment groups in each of the following two strata: 1) patients who had undergone one or more pituitary surgeries but had not been treated medically or 2) *de novo* patients presenting a visible pituitary adenoma on MRI who had refused pituitary surgery or for whom pituitary surgery was contraindicated.

The two treatment groups were well balanced in terms of baseline demographics and disease characteristics. 59.7% and 56% of patients in the pasireotide intramuscular use and octreotide intramuscular use treatment groups, respectively, were patients without previous pituitary surgery (*de novo*).

The starting dose was 40 mg for pasireotide intramuscular use and 20 mg for octreotide intramuscular use. Dose increase for efficacy was allowed at the discretion of the investigators after three and six months of treatment if biochemical parameters showed a mean GH ≥ 2.5 $\mu\text{g/l}$ and/or IGF-1 $> \text{ULN}$ (age and sex related). Maximum allowed dose was 60 mg for pasireotide intramuscular use and 30 mg for octreotide intramuscular use.

The primary efficacy endpoint was the proportion of patients with a reduction of mean GH level to < 2.5 $\mu\text{g/l}$ and the normalisation of IGF-1 to within normal limits (age and sex related) at month 12. The primary efficacy endpoint was met; the percentage of patients achieving biochemical control was 31.3% and 19.2% for pasireotide intramuscular use and octreotide intramuscular use, respectively, demonstrating a statistically significant superior result favouring pasireotide intramuscular use (p-value = 0.007) (Table 4).

Table 4 Key results at month 12 - phase III study in acromegaly patients

	Pasireotide intramuscular use n (%) N=176	Octreotide intramuscular use n (%) N=182	p-value
GH < 2.5 $\mu\text{g/l}$ and normalised IGF-1*	31.3%	19.2%	p=0.007
GH < 2.5 $\mu\text{g/l}$ and IGF-1 $\leq \text{ULN}$	35.8%	20.9%	-
Normalised IGF-1	38.6%	23.6%	p=0.002
GH < 2.5 $\mu\text{g/l}$	48.3%	51.6%	p=0.536

* Primary endpoint (patients with IGF-1 $<$ lower limit of normal (LLN) were not considered “responders”).

ULN = upper limit of normal

Biochemical control was achieved early in the study (i.e. month 3) by a higher proportion of patients in the pasireotide intramuscular use arm than in the octreotide intramuscular use arm (30.1% and 21.4%) and was maintained in all subsequent evaluations during the core phase.

At month 12, reduction in tumour volume was comparable between the treatment groups and in patients with and without previous pituitary surgery. The proportion of patients with a reduction of tumour volume greater than 20% at month 12 was 80.8% for pasireotide intramuscular use and 77.4% for octreotide intramuscular use.

Health-related quality of life measured by AcroQoL indicated statistically significant improvements in the Physical, Psychological-Appearance and Global scores in both treatment groups at month 12. Mean improvements from baseline were greater for pasireotide intramuscular use than for octreotide intramuscular use with no statistical significance.

Extension phase

At the end of the core phase, patients achieving biochemical control or benefiting from the treatment as assessed by the investigator could continue to be treated in the extension phase with the study treatment to which they were initially randomised.

During the extension phase, 74 patients continued receiving pasireotide intramuscular use and 46 patients continued with octreotide intramuscular use treatment. At month 25, 48.6% of patients (36/74) in the pasireotide intramuscular use group and 45.7% (21/46) in the octreotide intramuscular use group achieved biochemical control. The percentage of patients who had mean GH values < 2.5 $\mu\text{g/l}$ and normalisation of IGF-1 at the same time point was also comparable between the two

treatment arms.

During the extension phase, tumour volume continued to decrease.

Crossover phase

At the end of the core phase, patients not adequately responding to their initial therapy were allowed to switch treatment. 81 patients were crossed over from octreotide intramuscular use to pasireotide intramuscular use, and 38 patients were crossed over from pasireotide intramuscular use to octreotide intramuscular use.

Twelve months after crossover, the percentage of patients achieving biochemical control was 17.3% (14/81) for pasireotide intramuscular use and 0% (0/38) for octreotide intramuscular use. The percentage of patients achieving biochemical control, including those patients with IGF-1 <LLN was 25.9% in the pasireotide intramuscular use group and 0% in the octreotide intramuscular use group.

Further decrease in tumour volume was observed at month 12 after crossover for both treatment groups, and was higher in patients who crossed over to pasireotide intramuscular use (-24.7%) than in patients who crossed over to octreotide intramuscular use (-17.9%).

Cushing's disease study G2304

The efficacy and safety of pasireotide intramuscular use was evaluated in a phase III, multicentre study over a 12-month treatment period in Cushing's disease patients with persistent or recurrent disease or *de novo* patients for whom surgery was not indicated or who refused surgery. The eligibility criteria included a mean urinary free cortisol (mUFC) value of between 1.5 and 5 times upper limit of normal (ULN) at screening. The study enrolled 150 patients. The mean age was 35.8 years, and the majority of patients were female (78.8%). Most patients (82.0%) had undergone prior pituitary surgery, and the mean baseline mUFC was 470 nmol/24h (ULN: 166.5 nmol/24h).

Patients were randomised in a 1:1 ratio to a starting dose of either 10 mg or 30 mg pasireotide intramuscular use every 4 weeks. After four months of treatment, patients with mUFC $\leq 1.5 \times \text{ULN}$ continued on the blinded dose to which they were randomised, and patients with mUFC $> 1.5 \times \text{ULN}$ had their doses increased in a blinded manner from 10 mg to 30 mg, or from 30 mg to 40 mg, provided there were no tolerability concerns. Additional dose adjustments (up to a maximum of 40 mg) were allowed at months 7 and 9 of the core phase. The primary efficacy end point was the proportion of patients in each arm who achieved mean 24-hour UFC levels $\leq \text{ULN}$ after 7 months of treatment, regardless of prior dose increase. Secondary end points included changes from baseline in: 24-hour UFC, plasma ACTH, serum cortisol levels, and clinical signs and symptoms of Cushing's disease. All analyses were conducted based on the randomised dose groups.

Results

The study met the primary efficacy objective for both dose groups (lower bound of the 95% CI for the response rate of each treatment arm $> 15\%$). At month 7, a mUFC response was achieved in 41.9% and 40.8% of patients randomised to starting doses of 10 mg and 30 mg, respectively. The proportion of patients who either attained mUFC $\leq \text{ULN}$ or a mUFC reduction from baseline of at least 50% was 50.0% in the 10 mg dose group and 56.6% in the 30 mg dose groups (Table 5).

In both dose groups, Signifor resulted in a decrease in mean UFC after 1 month of treatment, and this was maintained over time. Decreases were also demonstrated by the overall percentage change from baseline in mean and median mUFC levels at month 7 and 12. Reductions in serum cortisol and plasma ACTH levels were also observed at month 7 and 12 for each dose group.

Table 5 Key results - phase III study in Cushing’s disease patients (intramuscular formulation)

	Pasireotide 10 mg N=74	Pasireotide 30 mg N=76
Percentage of patients with:		
mUFC \leq ULN at Month 7 (95% CI) *	41.9 (30.5, 53.9)	40.8 (29.7, 52.7)
mUFC \leq ULN and no prior dose increase at Month 7 (95% CI)	28.4 (18.5, 40.1)	31.6 (21.4, 43.3)
mUFC \leq ULN or \geq 50% decrease from baseline at month 7 (95% CI)	50.0 (38.1, 61.9)	56.6 (44.7, 67.9)
Median (min, max) % mUFC change from baseline at month 7	-47.9 (-94.2, 651.1)	-48.5 (-99.7, 181.7)
Median (min, max) % mUFC change from baseline at month 12	-52.5 (-96.9, 332.8)	-51.9 (-98.7, 422.3)

* Primary endpoint using LOCF (last observation carried forward)

mUFC: mean urinary free cortisol; ULN: upper limit of normal; CI: confidence interval

Decreases in systolic and diastolic blood pressure and in body weight were observed in both dose groups at month 7. Overall reductions in these parameters tended to be greater in patients that were mUFC responders. Similar trends were observed at month 12.

At month 7, most patients demonstrated either improvement in or stable signs of Cushing’s disease such as hirsutism, striae, bruising and muscle strength. Facial rubor improved in 43.5% (47/108) of patients, and more than a third of patients demonstrated improvement in supraclavicular fat pad (34.3%) and dorsal fat pad (34.6%). Similar results were also seen at month 12.

Health-related quality of life was assessed by a disease-specific patient-reported outcome measure (CushingQoL) and a generic quality of life measure (SF-12v2 General Health Survey). Improvements were observed in both dose groups for CushingQoL and the Mental Component Summary (MCS) of SF-12v2, but not for the Physical Component Summary (PCS) of SF-12v2.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Signifor in all subsets of the paediatric population in acromegaly and pituitary gigantism, and in pituitary dependant Cushing’s disease, overproduction of pituitary ACTH and pituitary dependant hyperadrenocorticism (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pasireotide for intramuscular use is formulated as microspheres for long-acting release. After a single injection, the plasma pasireotide concentration shows an initial burst release on the injection day, followed by a dip from day 2 to day 7, then a slow increase to maximum concentration around day 21, and a slow declining phase over the next weeks, concomitant with the terminal degradation phase of the polymer matrix of the dosage form.

Absorption

The relative bioavailability of pasireotide intramuscular use over pasireotide subcutaneous use is complete. No studies have been conducted to evaluate the absolute bioavailability of pasireotide in humans.

Distribution

In healthy volunteers, pasireotide intramuscular use is widely distributed with large apparent volume of distribution ($V_z/F > 100$ litres). Distribution between blood cells 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.

Based on *in vitro* data pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein). Based on *in vitro* data pasireotide is not a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1), OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1. At therapeutic dose levels pasireotide is also not an inhibitor of UGT1A1, OATP1B1 or 1B3, OAT1 or OAT3, OCT1 or OCT2, P-gp, BCRP, MRP2 and BSEP.

Biotransformation

Pasireotide is metabolically highly stable and *in vitro* data show that pasireotide is not a substrate, inhibitor or inducer of CYP450. In healthy volunteers, pasireotide is predominantly found in unchanged form in plasma, urine and faeces.

Elimination

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion), with a small contribution of the renal route. In a human ADME study 55.9±6.63% of the radioactive pasireotide subcutaneous dose was recovered over the first 10 days after administration, including 48.3±8.16% of the radioactivity in faeces and 7.63±2.03% in urine.

The apparent clearance (CL/F) of pasireotide intramuscular use in healthy volunteers is on average 4.5-8.5 litres/h. Based on population pharmacokinetic (PK) analyses, the estimated CL/F was approximately 4.8 to 6.5 litres/h for typical Cushing's disease patients, and approximately 5.6 to 8.2 litres/h for typical acromegaly patients.

Linearity and time dependency

Pharmacokinetic steady state for pasireotide intramuscular use is achieved after three months. Following multiple monthly doses, pasireotide intramuscular use demonstrates approximately dose-proportional pharmacokinetic exposures in the dose range of 10 mg to 60 mg every 4 weeks.

Special populations

Paediatric population

No studies have been performed in paediatric patients.

Patients with renal impairment

Renal clearance has a minor contribution to the elimination of pasireotide in humans. In a clinical study with single subcutaneous dose administration of 900 µg pasireotide in subjects with impaired renal function, renal impairment of mild, moderate or severe degree, or end stage renal disease (ESRD) did not have a significant impact on total pasireotide plasma exposure. The unbound plasma pasireotide exposure ($AUC_{inf,u}$) was increased in subjects with renal impairment (mild: 33%; moderate: 25%, severe: 99%, ESRD: 143%) compared to control subjects.

Patients with hepatic impairment

No clinical studies in subjects with liver impairment have been performed with pasireotide intramuscular use. In a clinical study of a single subcutaneous dose of pasireotide in subjects with impaired hepatic function, statistically significant differences were found in subjects with moderate and severe hepatic impairment (Child-Pugh B and C). In subjects with moderate and severe hepatic impairment, AUC_{inf} was increased 60% and 79%, C_{max} was increased 67% and 69%, and CL/F was decreased 37% and 44%, respectively.

Elderly patients (≥65 years)

Age is not a significant covariate in the population pharmacokinetic analysis of patients.

Demographics

Population PK analyses of pasireotide intramuscular use suggest that race does not influence PK parameters. PK exposures had a slight correlation with body weight in the study with medical treatment naïve patients, but not in the study with inadequately controlled patients. Female acromegaly patients had a higher exposure of 32% and 51% compared to male patients in studies with medical treatment naïve patients and inadequately controlled patients, respectively; these differences in exposure were not clinically relevant based on efficacy and safety data.

5.3 Preclinical safety data

Non-clinical safety data from studies performed with pasireotide administered via the subcutaneous route reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Additionally, tolerability and repeated dose toxicity studies were conducted with pasireotide via the intramuscular route. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Poly(D,L-lactide-co-glycolide) (50-60:40-50)

Poly(D,L-lactide-co-glycolide) (50:50)

Solvent

Carmellose sodium

Mannitol

Poloxamer 188

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

6.5 Nature and contents of container

Powder: brownish vial (glass) with rubber stopper (chlorobutyl rubber), containing the active substance (pasireotide).

Solvent: colourless pre-filled syringe (glass) with front and plunger stopper (chlorobutyl rubber), containing 2 ml solvent.

Unit packs (all strengths): each unit pack contains a blister tray with one injection kit (one vial and, in a separate sealed section, one pre-filled syringe, one vial adapter and one safety-engineered needle for injection).

Multipacks (40 mg and 60 mg strengths only): each multipack contains 3 intermediate cartons, each containing a blister tray with one injection kit (one vial and, in a separate sealed section, one pre-filled syringe, one vial adapter and one safety engineered needle for injection).

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal and other handling

There are two critical steps in the reconstitution of Signifor. **Not following them could result in failure to deliver the injection appropriately.**

- **The injection kit must reach room temperature.** Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the solvent, **shake the vial moderately** for a minimum of 30 seconds **until a uniform suspension is formed.**

Included in the injection kit:

- a One vial containing the powder
- b One pre-filled syringe containing the solvent
- c One vial adapter for medicinal product reconstitution
- d One safety injection needle (20G x 1.5")

Follow the instructions below carefully to ensure proper reconstitution of Signifor powder and solvent for suspension for injection before deep intramuscular injection.

Signifor suspension must only be prepared immediately before administration.

Signifor should only be administered by a trained healthcare professional.

To prepare Signifor for deep intramuscular injection, please adhere to the following instructions:

1. Remove the Signifor injection kit from refrigerated storage. **ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes**

- before reconstitution, but do not exceed 24 hours.** If not used within 24 hours, the injection kit can be returned to the fridge.
2. Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.
 3. Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.
 4. Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by a “click”.
 5. Remove the packaging from the vial adapter by lifting it straight up.
 6. Remove the cap from the syringe pre-filled with solvent and **screw** the syringe onto the vial adapter.
 7. Slowly push the plunger all the way down to transfer all the solvent in the vial.
 8. **ATTENTION:** Keep the plunger pressed and shake the vial **moderately for a minimum of 30 seconds** so that the powder is completely suspended. **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**
 9. Turn syringe and vial upside down, **slowly** pull the plunger back and draw the entire content from the vial into the syringe.
 10. Unscrew the syringe from the vial adapter.
 11. Screw the safety injection needle onto the syringe.
 12. Pull the protective cover straight off the needle. To avoid sedimentation, you may gently shake the syringe to maintain a uniform suspension. Gently tap the syringe to remove any visible bubbles and expel them from the syringe. The reconstituted Signifor is now ready for **immediate** administration.
 13. Signifor must be given only by deep intramuscular injection. Prepare the injection site with an alcohol wipe. Insert the needle fully into the left or right gluteus at a 90° angle to the skin. Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated). Slowly depress the plunger until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard.
 14. Activate the safety guard over the needle, in one of the two methods shown:
 - either press the hinged section of the safety guard down onto a hard surface
 - or push the hinge forward with your fingerAn audible “click” confirms proper activation. Dispose of syringe immediately in a sharps container.

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

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

Signifor 10 mg powder and solvent for suspension for injection
EU/1/12/753/018

Signifor 20 mg powder and solvent for suspension for injection
EU/1/12/753/013

Signifor 30 mg powder and solvent for suspension for injection
EU/1/12/753/019

Signifor 40 mg powder and solvent for suspension for injection
EU/1/12/753/014-015

Signifor 60 mg powder and solvent for suspension for injection
EU/1/12/753/016-017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2012
Date of latest renewal: 18 November 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

Recordati Rare Diseases
Eco River Parc
30 rue des Peupliers
92000 Nanterre
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.3 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.3 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/001 6 ampoules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.3 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.3 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/002	18 ampoules (3x6)
EU/1/12/753/003	30 ampoules (5x6)
EU/1/12/753/004	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.3 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.3 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.3 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 18 (3 packs of 6) ampoules.

Multipack: 30 (5 packs of 6) ampoules.

Multipack: 60 (10 packs of 6) ampoules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/002	18 ampoules (3x6)
EU/1/12/753/003	30 ampoules (5x6)
EU/1/12/753/004	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 0.3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 0.3 mg injection
pasireotide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.6 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.6 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/005 6 ampoules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.6 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.6 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/006	18 ampoules (3x6)
EU/1/12/753/007	30 ampoules (5x6)
EU/1/12/753/008	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.6 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.6 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.6 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 18 (3 packs of 6) ampoules.

Multipack: 30 (5 packs of 6) ampoules.

Multipack: 60 (10 packs of 6) ampoules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/006	18 ampoules (3x6)
EU/1/12/753/007	30 ampoules (5x6)
EU/1/12/753/008	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 0.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 0.6 mg injection
pasireotide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.9 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.9 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/009 6 ampoules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.9 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.9 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 ampoules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/010	18 ampoules (3x6)
EU/1/12/753/011	30 ampoules (5x6)
EU/1/12/753/012	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Signifor 0.9 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.9 mg solution for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for injection contains 0.9 mg pasireotide (as pasireotide diaspertate).

3. LIST OF EXCIPIENTS

Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 18 (3 packs of 6) ampoules.

Multipack: 30 (5 packs of 6) ampoules.

Multipack: 60 (10 packs of 6) ampoules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/010	18 ampoules (3x6)
EU/1/12/753/011	30 ampoules (5x6)
EU/1/12/753/012	60 ampoules (10x6)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 0.9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 0.9 mg injection
pasireotide
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Signifor 10 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 10 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder

1 pre-filled syringe with 2 ml solvent

1 safety-engineered needle

1 vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 10 mg powder for injection
pasireotide
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

Solvent for Signifor

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Signifor 20 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 20 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder

1 pre-filled syringe with 2 ml solvent

1 safety-engineered needle

1 vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 20 mg powder for injection
pasireotide
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

Solvent for Signifor

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Signifor 30 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 30 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder

1 pre-filled syringe with 2 ml solvent

1 safety-engineered needle

1 vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 30 mg powder for injection
pasireotide
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mg

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

Solvent for Signifor

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Signifor 40 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 40 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder

1 pre-filled syringe with 2 ml solvent

1 safety-engineered needle

1 vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 40 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 40 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder + 1 pre-filled syringe with 2 ml solvent+ 1 safety-engineered needle + 1 vial adapter.
Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/015

Multipack containing 3 intermediate cartons

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 40 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 40 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 40 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

Multipack: 3 packs of 1 injection kit

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/015

Multipack containing 3 intermediate cartons

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 40 mg powder for injection
pasireotide
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

Solvent for Signifor

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Signifor 60 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 60 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder

1 pre-filled syringe with 2 ml solvent

1 safety-engineered needle

1 vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 60 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 60 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

1 vial of powder + 1 pre-filled syringe with 2 ml solvent+ 1 safety-engineered needle + 1 vial adapter.
Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/017

Multipack containing 3 intermediate cartons

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 60 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Signifor 60 mg powder and solvent for suspension for injection
pasireotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 60 mg pasireotide (as pasireotide pamoate).

3. LIST OF EXCIPIENTS

Also contains:

Powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).

Solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection

Multipack: 3 packs of 1 injection kit

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.

Read the package leaflet before use.

Intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/017 Multipack containing 3 intermediate cartons

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Signifor 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Signifor 60 mg powder for injection
pasireotide
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 mg

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

Solvent for Signifor

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Signifor 0.3 mg solution for injection
Signifor 0.6 mg solution for injection
Signifor 0.9 mg solution for injection
pasireotide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Signifor is and what it is used for
2. What you need to know before you use Signifor
3. How to use Signifor
4. Possible side effects
5. How to store Signifor
6. Contents of the pack and other information

1. What Signifor is and what it is used for

Signifor is a medicine that contains the active substance pasireotide. It is used to treat Cushing's disease in adult patients for whom surgery is not an option or for whom surgery has failed.

Cushing's disease is caused by an enlargement in the pituitary gland (a gland at the base of the brain) called a pituitary adenoma. This leads the body to over-produce a hormone called adrenocorticotrophic hormone (ACTH), which in turn results in over-production of another hormone called cortisol.

The human body naturally produces a substance called somatostatin, which blocks the production of certain hormones, including ACTH. Pasireotide works in a very similar way to somatostatin. Signifor is thus able to block the production of ACTH, helping to control the over-production of cortisol and improve the symptoms of Cushing's disease.

If you have any questions about how Signifor works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use Signifor

Do not use Signifor

- if you are allergic to pasireotide or any of the other ingredients of this medicine (listed in section 6).
- if you have severe liver problems.

Warnings and precautions

Talk to your doctor before using Signifor if you currently have or have ever had:

- problems with your blood sugar levels, whether too high (as in hyperglycaemia/diabetes) or too low (hypoglycaemia);
- heart problems such as a recent heart attack, congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body) or sudden and oppressive chest pain (usually felt as pressure, heaviness, tightening, squeezing or aching across the chest);

- a heart rhythm disorder, such as an irregular heartbeat or an abnormal electrical signal called “prolongation of the QT interval”, or “QT prolongation”;
- low levels of potassium or magnesium in your blood;
- gallstones.

During your treatment with Signifor

- Signifor controls over-production of cortisol. The control may be too strong and you may experience signs or symptoms associated with a lack of cortisol, such as extreme weakness, tiredness, weight loss, nausea, vomiting or low blood pressure. If this happens, tell your doctor immediately.
- Signifor may cause your blood sugar to increase. Your doctor may want to monitor your blood sugar and start treatment with or adjust your antidiabetic medicine.
- Signifor may lower your heart rate. Your doctor may wish to monitor your heart rate using a machine that measures electrical activity of the heart (an “ECG”, or electrocardiogram). If you are using medicine to treat a heart condition, your doctor may also need to adjust its dosage.
- your doctor may also wish to check your gallbladder, liver enzymes and pituitary hormones periodically, since these might all be affected by this medicine.

Children and adolescents

Do not give this medicine to children and adolescents below 18 years old because no data are available in this age group.

Other medicines and Signifor

Signifor may affect the way some other medicines work. If you are using other medicines at the same time as Signifor (including medicines obtained without a prescription), your doctor may need to monitor your heart more carefully or change the dose of Signifor or the other medicines. Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Especially, tell your doctor if you are using:

- medicines to treat irregular heartbeat, such as medicines containing disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide, amiodarone or dronedarone;
- medicines to treat bacterial infections (by mouth: clarithromycin, moxifloxacin; via injection: erythromycin, pentamidine);
- medicines to treat fungal infections (ketoconazole, except in shampoo);
- medicines to treat certain psychiatric disorders (chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone);
- medicines to treat hay fever and other allergies (terfenadine, astemizole, mizolastine);
- medicines used in the prevention or treatment of malaria (chloroquine, halofantrine, lumefantrine);
- medicines to control blood pressure such as:
 - beta blockers (metoprolol, carteolol, propranolol, sotalol)
 - calcium channel blockers (bepridil, verapamil, diltiazem)
 - cholinesterase inhibitors (rivastigmine, physostigmine);
- medicines to control the balance of electrolytes (potassium, magnesium) in your body.

It is particularly important that you mention any of the following medicines:

- ciclosporin (used in organ transplantation to reduce the activity of the immune system);
- medicines to treat blood sugar levels that are too high (as in diabetes) or too low (hypoglycaemia), such as:
 - insulin;
 - metformin, liraglutide, vildagliptin, nateglinide (antidiabetic medicines).

Pregnancy, breast-feeding and fertility

Ask your doctor or pharmacist for advice before using any medicine.

- You should not use Signifor during pregnancy unless clearly necessary. If you are pregnant or think that you may be, it is important to tell your doctor who will discuss with you whether you can use Signifor during your pregnancy.
- You should not breast-feed while using Signifor. It is not known whether Signifor passes into

breast milk.

- If you are a sexually active woman, you should use an effective method of contraception during treatment. Ask your doctor about the need for contraception before taking this medicine.

Driving and using machines

Signifor may have a minor effect on the ability to drive and use machines, because some of the side effects you may experience while using Signifor, such as dizziness, headache and tiredness, may reduce your ability to drive and use machines safely.

Important information about some of the ingredients of Signifor

Signifor contains less than 1 mmol sodium (23 mg) per dose, which means it is essentially “sodium-free”.

3. How to use Signifor

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. This medicine comes in an ampoule, i.e. a small glass container.

How much Signifor to use

The recommended dose is one ampoule of Signifor 0.6 mg twice a day. Using Signifor at the same time each day will help you remember when to use your medicine. After you have started treatment, your doctor may also decide to increase your dose to one ampoule of Signifor 0.9 mg twice a day.

If side effects occur your doctor may temporarily reduce your dose by 0.3 mg per injection.

If you have liver disease before you start Signifor treatment, your doctor may want to start your treatment with a dose of one ampoule of Signifor 0.3 mg twice a day.

Ampoules of Signifor of different strengths (0.3 mg, 0.6 mg and 0.9 mg) are available to match the specific dose prescribed by your doctor.

Your doctor will check regularly how you respond to the treatment with Signifor and determine which dose is best for you.

How to use Signifor

Your doctor or nurse will instruct you on how to inject yourself with Signifor. You should also read the instructions at the end of this leaflet. If you have any questions, contact your doctor, nurse or pharmacist.

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

Do not use Signifor if you notice the solution is not clear or contains particles. The solution should be free of visible particles, clear and colourless.

How long to use Signifor

You should continue using Signifor for as long as your doctor tells you to.

If you use more Signifor than you should

If you accidentally use more Signifor than your doctor prescribed, immediately contact your doctor, nurse or pharmacist.

If you forget to use Signifor

Do not inject a double dose of Signifor to make up for a forgotten dose. If you forgot to inject a dose

of Signifor, simply inject the next dose at the scheduled time.

If you stop using Signifor

If you interrupt your treatment with Signifor your cortisol level may increase again and your symptoms may come back. Therefore, do not stop using Signifor unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious. Tell your doctor straight away if you get any of the following:

Very common (may affect more than 1 in 10 people)

- Changed level of sugar in the blood. You may experience excessive thirst, high urine output, increased appetite with weight loss, tiredness, nausea, vomiting, abdominal pain.
- Gallstones or associated complications. You may experience fever, chills, yellowing of skin/eyes, sudden back pain or pain in the right side of your abdomen.
- Extreme tiredness.

Common (may affect up to 1 in 10 people)

- Low cortisol levels. You may experience extreme weakness, tiredness, weight loss, nausea, vomiting and low blood pressure.
- Slow heart beat.
- Low blood pressure. You may experience dizziness, light headedness and dizziness or fainting on standing up.
- Problems with bile flow (cholestasis). You may experience yellowing of the skin, dark urine, pale stools and itching.
- Inflammation of the gallbladder (cholecystitis).

Other side effects of Signifor may include:

Very common (may affect more than 1 in 10 people)

- Diarrhoea
- Nausea
- Stomach pain
- Pain at the injection site

Common (may affect up to 1 in 10 people)

- Prolonged QT interval (an abnormal electrical signal in your heart that can be seen in tests)
- Loss of appetite
- Vomiting
- Headache
- Dizziness
- Hair loss
- Itching (pruritus)
- Muscle pain (myalgia)
- Joint pain (arthralgia)
- Abnormal results of liver function tests
- Abnormal results of pancreatic function tests
- Abnormal blood coagulation properties

Uncommon (may affect up to 1 in 100 people)

- Low level of red blood cells (anaemia)

Not known (frequency cannot be estimated from the available data)

- Increased levels of ketone bodies (a group of substances produced in the liver) in your urine or blood (diabetic ketoacidosis) as a complication of an increased level of sugar in your blood. You may experience fruity scented breath, trouble breathing and confusion.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Signifor

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the ampoule label and carton after “EXP”. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Signifor contains

- The active substance is pasireotide.
Signifor 0.3 mg: One ampoule of 1 ml solution contains 0.3 mg pasireotide (as pasireotide diaspertate).
Signifor 0.6 mg: One ampoule of 1 ml solution contains 0.6 mg pasireotide (as pasireotide diaspertate).
Signifor 0.9 mg: One ampoule of 1 ml solution contains 0.9 mg pasireotide (as pasireotide diaspertate).
- The other ingredients are mannitol, tartaric acid, sodium hydroxide and water for injections.

What Signifor looks like and contents of the pack

Signifor solution for injection is a clear, colourless solution in an ampoule. Each ampoule contains 1 ml of solution for injection.

Signifor is available in packs containing 6 ampoules or in multipacks containing 18 (3 packs of 6), 30 (5 packs of 6) or 60 (10 packs of 6) ampoules.

Not all strengths or pack sizes may be marketed in your country.

Marketing Authorisation Holder

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

Manufacturer

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

Recordati Rare Diseases
Eco River Parc
30 rue des Peupliers
92000 Nanterre
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Recordati
Tél/Tel: +32 2 46101 36

Lietuva

Recordati AB.
Tel: + 46 8 545 80 230
Švedija

България

Recordati Rare Diseases
Тел.: +33 (0)1 47 73 64 58
Франция

Luxembourg/Luxemburg

Recordati
Tél/Tel: +32 2 46101 36
Belgique/Belgien

Česká republika

Recordati Rare Diseases
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Francie

Magyarország

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Franciaország

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Deutschland

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Francja

France

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Tél: +33 (0)1 47 73 64 58

Hrvatska

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Francuska

Ireland

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Recordati AB.
Tel: + 46 8 545 80 230
Zviedrija

Portugal

Jaba Recordati S.A.
Tel: +351 21 432 95 00

România

Recordati Rare Diseases
Tel: +33 (0)1 47 73 64 58
Franța

Slovenija

Recordati Rare Diseases
Tel: +33 (0)1 47 73 64 58
Francija

Slovenská republika

Recordati Rare Diseases
Tel: +33 (0)1 47 73 64 58
Francúzsko

Suomi/Finland

Recordati AB.
Puh/Tel : +46 8 545 80 230
Sverige

Sverige

Recordati AB.
Tel : +46 8 545 80 230

United Kingdom (Northern Ireland)

Recordati Rare Diseases UK Ltd.
Tel: +44 (0)1491 414333

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

INSTRUCTIONS FOR USE OF SIGNIFOR SOLUTION FOR INJECTION

This medicine comes in an ampoule, i.e. a small glass container. Signifor should be administered using sterile disposable syringes and injection needles.

Your doctor or nurse 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 giving yourself the injection or if you have any questions, please ask your doctor or nurse 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 Signifor ampoules according to the storage conditions listed on the box.

Important safety information

Caution: Keep the ampoules out of the reach of children.

What do I need

To give yourself an injection you will need:

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

Getting started

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

- Wash your hands thoroughly with soap and water.
- Use new disposable needles and syringes every time you give yourself an injection. Use syringes and needles only once. **Never** share needles and syringes.
- Take the ampoule out of the box.
- 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 pack to the pharmacy.

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

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

Check the expiry date and the dose

Check the expiry date which is stated on the ampoule label (after "EXP") and check that the ampoule contains the dose that your doctor has prescribed.

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

How to inject Signifor



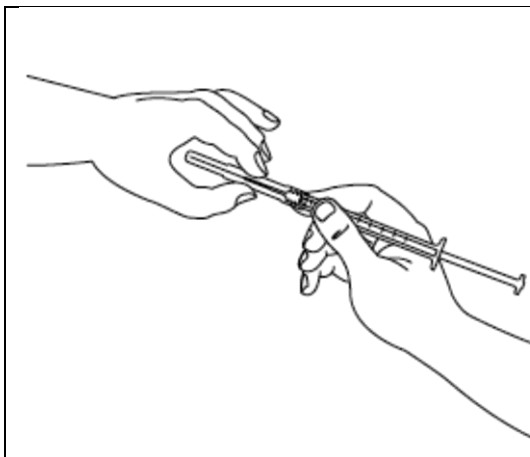
Step 1:

Signifor solution for injection is filled in a break-off ampoule. The coloured dot on the top part marks the position of the breaking point 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.



Step 2:

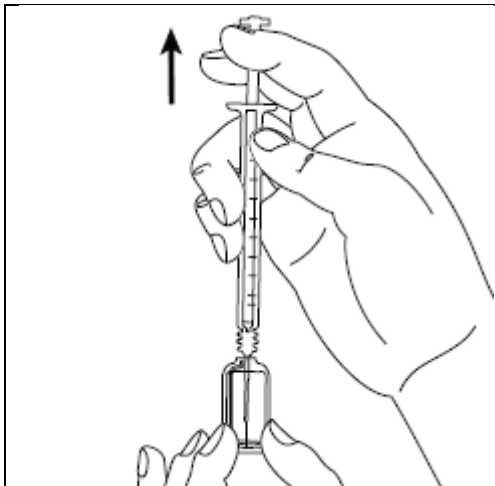
Recommended procedure: hold the ampoule in an upright position with the coloured dot facing away from you. Hold the base of the ampoule in one hand. Keeping your thumbs together above and below the neck, break off the top of the ampoule at the breaking point. Once the ampoule is open, put it upright 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.

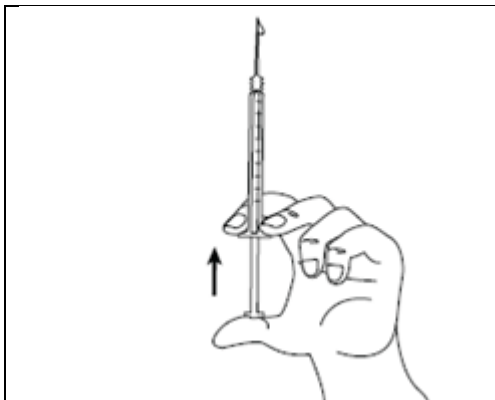
Before you proceed to step 4, clean the injection site with an alcohol wipe.



Step 4:

Remove the cover from the needle. Put the needle into the ampoule and pull the plunger to draw up the entire contents of the ampoule into the syringe.

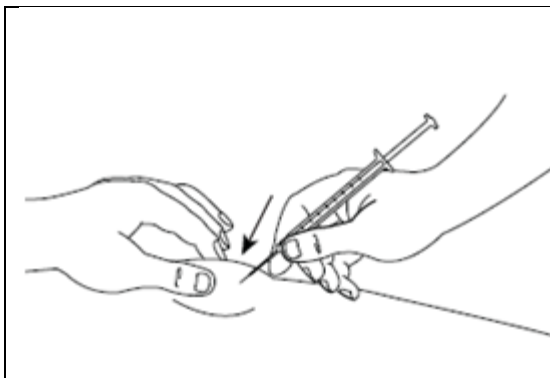
If you have been told to use two needles, you should now replace the long needle with the short one.



Step 5:

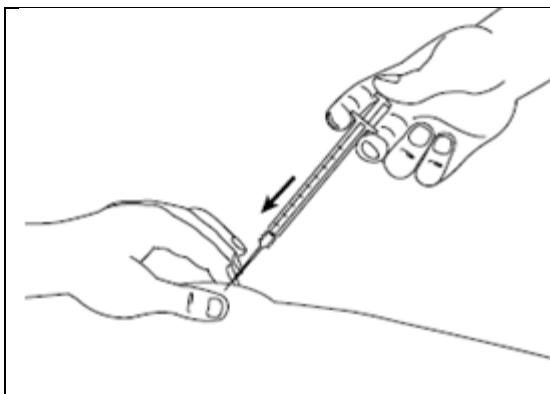
Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger. Tap the syringe with your fingers to get rid of air bubbles. Make sure there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.

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



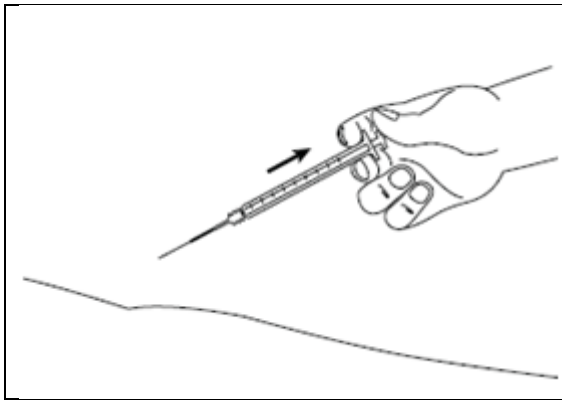
Step 6:

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.



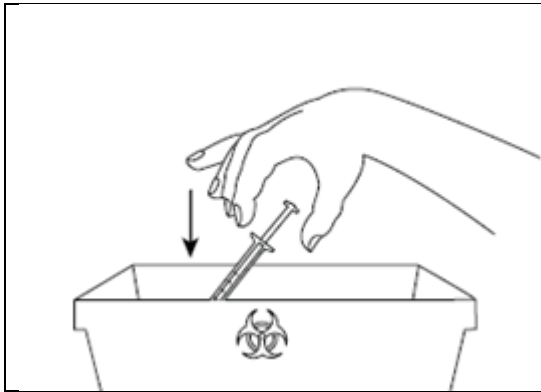
Step 7:

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



Step 8:

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



Step 9:

Dispose of the used syringe and needle immediately in a sharps container or other rigid closed disposal container. Any unused product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Signifor 10 mg powder and solvent for suspension for injection
Signifor 20 mg powder and solvent for suspension for injection
Signifor 30 mg powder and solvent for suspension for injection
Signifor 40 mg powder and solvent for suspension for injection
Signifor 60 mg powder and solvent for suspension for injection
pasireotide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Signifor is and what it is used for
2. What you need to know before you use Signifor
3. How to use Signifor
4. Possible side effects
5. How to store Signifor
6. Contents of the pack and other information

1. What Signifor is and what it is used for

Signifor is a medicine that contains the active substance pasireotide. It is used to treat acromegaly in adult patients. It is also used to treat Cushing's disease in adult patients for whom surgery is not an option or for whom surgery has failed.

Acromegaly

Acromegaly is caused by a type of tumour called a pituitary adenoma which develops in the pituitary gland at the base of the brain. The adenoma leads the body to over-produce hormones that control growth of tissues, organs and bones, resulting in an increase in the size of bones and tissues, especially in the hands and feet.

Signifor reduces the production of these hormones and possibly also the size of the adenoma. As a result, it reduces the symptoms of acromegaly, which include headache, increased sweating, numbness of the hands and feet, tiredness and joint pain.

Cushing's disease

Cushing's disease is caused by an enlargement in the pituitary gland (a gland at the base of the brain) called a pituitary adenoma. This leads the body to over-produce a hormone called adrenocorticotrophic hormone (ACTH), which in turn results in over-production of another hormone called cortisol.

The human body naturally produces a substance called somatostatin, which blocks the production of certain hormones, including ACTH. Pasireotide works in a very similar way to somatostatin. Signifor is thus able to block the production of ACTH, helping to control the over production of cortisol and improve the symptoms of Cushing's disease.

If you have any questions about how Signifor works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use Signifor

Do not use Signifor

- if you are allergic to pasireotide or any of the other ingredients of this medicine (listed in section 6).
- if you have severe liver problems.

Warnings and precautions

Talk to your doctor before using Signifor if you currently have or have ever had:

- problems with your blood sugar levels, whether too high (as in hyperglycaemia/diabetes) or too low (hypoglycaemia);
- heart problems such as a recent heart attack, congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body) or sudden and oppressive chest pain (usually felt as pressure, heaviness, tightening, squeezing or aching across the chest);
- a heart rhythm disorder, such as an irregular heartbeat or an abnormal electrical signal called “prolongation of the QT interval”, or “QT prolongation”;
- low levels of potassium or magnesium in your blood;
- gallstones;
- or if you are taking anticoagulants (medicines used to reduce the clotting ability of the blood), your doctor will monitor your coagulation parameters and may adjust your anticoagulant dose.

During your treatment with Signifor:

- Signifor may cause your blood sugar to increase. Your doctor may want to monitor your blood sugar and start treatment with or adjust your antidiabetic medicine.
- Signifor controls over-production of cortisol. The control may be too strong and you may experience signs or symptoms associated with a lack of cortisol, such as extreme weakness, tiredness, weight loss, nausea, vomiting or low blood pressure. If this happens, tell your doctor immediately.
- Signifor may lower your heart rate. Your doctor may wish to monitor your heart rate using a machine that measures electrical activity of the heart (an “ECG”, or electrocardiogram). If you are using medicine to treat a heart condition, your doctor may also need to adjust its dosage.
- your doctor may also wish to check your gallbladder, liver enzymes and pituitary hormones periodically, since these might all be affected by this medicine.

Children and adolescents

Do not give this medicine to children and adolescents below 18 years old because no data are available in this age group.

Other medicines and Signifor

Signifor may affect the way some other medicines work. If you are using other medicines at the same time as Signifor (including medicines obtained without a prescription), your doctor may need to monitor your heart more carefully or change the dose of Signifor or the other medicines. Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Especially, tell your doctor if you are using:

- medicines used in organ transplantation to reduce the activity of the immune system (ciclosporin);
- medicines to treat blood sugar levels that are too high (as in diabetes) or too low (hypoglycaemia) such as:
 - insulin
 - metformin, liraglutide, vildagliptin, nateglinide (antidiabetic medicines);
- medicines to treat irregular heartbeat, such as medicines containing disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide, amiodarone or dronedarone;
- medicines to treat bacterial infections (by mouth: clarithromycin, moxifloxacin; via injection: erythromycin, pentamidine);
- medicines to treat fungal infections (ketoconazole, except in shampoo);
- medicines to treat certain psychiatric disorders (chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone);

- medicines to treat hay fever and other allergies (terfenadine, astemizole, mizolastine);
- medicines used in the prevention or treatment of malaria (chloroquine, halofantrine, lumefantrine);
- medicines to control blood pressure such as:
 - beta blockers (metoprolol, carteolol, propranolol, sotalol)
 - calcium channel blockers (bepridil, verapamil, diltiazem)
 - cholinesterase inhibitors (rivastigmine, physostigmine);
- medicines to control the balance of electrolytes (potassium, magnesium) in your body.

Pregnancy, breast-feeding and fertility

Ask your doctor or pharmacist for advice before using any medicine.

- You should not use Signifor during pregnancy unless clearly necessary. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- If you are breast-feeding, ask your doctor for advice before taking this medicine, as it is not known whether Signifor passes into breast milk.
- If you are a sexually active woman, you should use an effective method of contraception during treatment. Ask your doctor about the need for contraception before taking this medicine.

Driving and using machines

Signifor may have a minor effect on the ability to drive and use machines, because some of the side effects you may experience while using Signifor, such as headache, dizziness and tiredness, may reduce your ability to drive and use machines safely.

Important information about some of the ingredients of Signifor

Signifor contains less than 1 mmol sodium (23 mg) per dose, which means it is essentially “sodium-free”.

3. How to use Signifor

This medicine will be given to you by a trained healthcare professional.

How much Signifor to use

Acromegaly

The recommended starting dose of Signifor in acromegaly is 40 mg every 4 weeks. After you have started treatment, your doctor may reassess your dose. This may involve measuring the levels of growth hormone or other hormones in your blood. Depending on the results and how you are feeling, the dose of Signifor given in each injection may need to be reduced or increased. The dose should not exceed 60 mg. If you have liver disease before you start Signifor treatment for acromegaly, your doctor may want to start your treatment with a dose of 20 mg.

Cushing’s disease

The usual starting dose of Signifor in Cushing’s disease is 10 mg every 4 weeks. After you have started treatment, your doctor may reassess your dose. This may involve measuring the levels of cortisol in your blood or urine. Depending on the results and how you are feeling, the dose of Signifor given in each injection may need to be reduced or increased. The dose should not exceed 40 mg.

Your doctor will check regularly how you respond to the treatment with Signifor and determine which dose is best for you.

How to use Signifor

Your doctor or nurse will inject Signifor. If you have any questions, contact your doctor, nurse or pharmacist.

Signifor is intended for intramuscular use. This means that it is injected through a needle into the

muscles of your buttocks.

How long to use Signifor

This is a long-term treatment, possibly lasting for years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect. Your treatment with Signifor should continue for as long as your doctor tells you that it is necessary.

If you stop using Signifor

If you interrupt your treatment with Signifor your symptoms may come back. Therefore, do not stop using Signifor unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious. Tell your doctor straight away if you get any of the following:

Very common (may affect more than 1 in 10 people)

- High level of sugar in the blood. You may experience excessive thirst, high urine output, increased appetite with weight loss, tiredness, nausea, vomiting, abdominal pain
- Gallstones or associated complications. You may experience fever, chills, yellowing of skin/eyes, sudden back pain or pain in the right side of your abdomen.

Common (may affect up to 1 in 10 people)

- Low cortisol levels. You may experience extreme weakness, tiredness, weight loss, nausea, vomiting and low blood pressure.
- Slow heart beat.
- Prolonged QT interval (an abnormal electrical signal in your heart that can be seen in tests).
- Problems with bile flow (cholestasis). You may experience yellowing of the skin, dark urine, pale stools, and itching.
- Inflammation of the gallbladder (cholecystitis).

Other side effects of Signifor may include:

Very common (may affect more than 1 in 10 people)

- Diarrhoea
- Nausea
- Abdominal pain
- Fatigue

Common (may affect up to 1 in 10 people)

- Tiredness, fatigue, pale skin (signs of low level of red blood cells)
- Loss of appetite
- Headache
- Bloating
- Vomiting
- Dizziness
- Pain, discomfort, pruritis and swelling at the injection site
- Change in liver function test results
- Abnormal blood test results (sign of high level of creatine phosphokinase, glycosylated haemoglobin, lipase in the blood)
- Hair loss

Uncommon (may affect up to 1 in 100 people)

- Change in pancreatic function blood test results (amylase)
- Abnormal blood coagulation properties

Not known (frequency cannot be estimated from the available data)

- Increased levels of ketone bodies (a group of substances produced in the liver) in your urine or blood (diabetic ketoacidosis) as a complication of an increased level of sugar in your blood. You may experience fruity scented breath, trouble breathing and confusion.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Signifor

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton, vial and pre-filled syringe after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Signifor contains

- The active substance is pasireotide.
Signifor 10 mg: each vial contains 10 mg pasireotide (as pasireotide pamoate).
Signifor 20 mg: each vial contains 20 mg pasireotide (as pasireotide pamoate).
Signifor 30 mg: each vial contains 30 mg pasireotide (as pasireotide pamoate).
Signifor 40 mg: each vial contains 40 mg pasireotide (as pasireotide pamoate).
Signifor 60 mg: each vial contains 60 mg pasireotide (as pasireotide pamoate).
- The other ingredients are:
 - In the powder: poly(D,L-lactide-co-glycolide) (50-60:40-50), poly(D,L-lactide-co-glycolide) (50:50).
 - In the solvent: carmellose sodium, mannitol, poloxamer 188, water for injections.

What Signifor looks like and contents of the pack

Signifor powder is a slightly yellowish to yellowish powder in a vial. The solvent is a clear, colourless to slightly yellow or slightly brown solution in a pre-filled syringe.

Signifor 10 mg is available in unit packs containing one vial of powder with 10 mg pasireotide and one pre filled syringe with 2 ml solvent.

Signifor 20 mg is available in unit packs containing one vial of powder with 20 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Signifor 30 mg is available in unit packs containing one vial of powder with 30 mg pasireotide and one pre filled syringe with 2 ml solvent.

Signifor 40 mg is available in unit packs containing one vial of powder with 40 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Signifor 60 mg is available in unit packs containing one vial of powder with 60 mg pasireotide and one pre-filled syringe with 2 ml solvent.

Each unit pack contains the vial and pre-filled syringe in a sealed blister tray with one vial adapter and

one safety-engineered needle for injection.

Signifor 40 mg and Signifor 60 mg are also available in multipacks containing 3 intermediate packs.

Not all strengths or pack sizes may be marketed in your country.

Marketing Authorisation Holder

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

Manufacturer

Recordati Rare Diseases
Immeuble Le Wilson
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92800 Puteaux
France

Recordati Rare Diseases
Eco River Parc
30 rue des Peupliers
92000 Nanterre
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

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Tél/Tel: +32 2 46101 36

Lietuva

Recordati AB.
Tel: + 46 8 545 80 230
Švedija

България

Recordati Rare Diseases
Тел.: +33 (0)1 47 73 64 58
Франция

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Francie

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Franța

Slovenija

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Francija

Slovenská republika

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Sverige

Sverige

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Recordati Rare Diseases UK Ltd.
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: <http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

INSTRUCTIONS FOR USE OF SIGNIFOR POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION

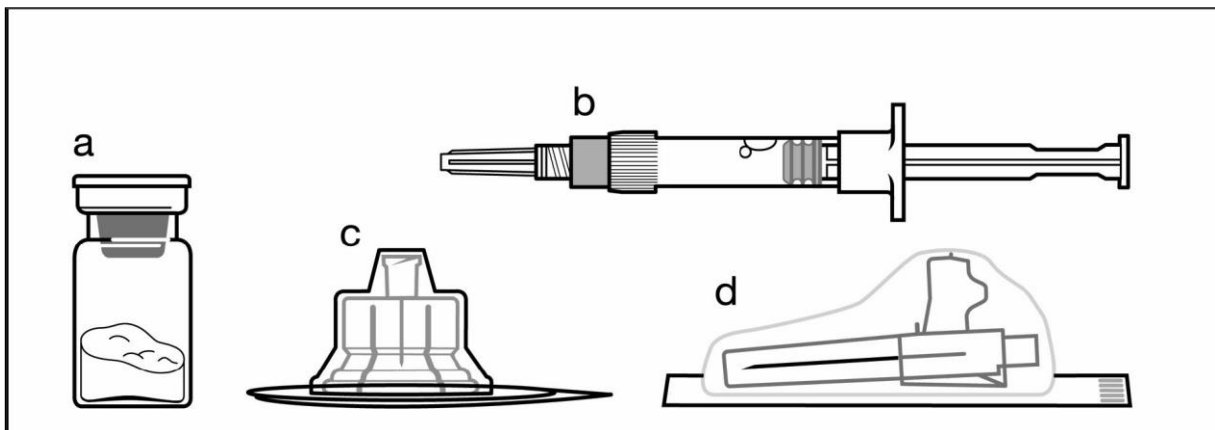
FOR DEEP INTRAMUSCULAR INJECTION ONLY.

ATTENTION:

There are two critical steps in the reconstitution of Signifor. **Not following them could result in failure to deliver the injection appropriately.**

- **The injection kit must reach room temperature.** Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the solvent, **shake the vial moderately** for a minimum of 30 seconds **until a uniform suspension is formed.**

Included in the injection kit:



- a One vial containing the powder
- b One pre-filled syringe containing the solvent
- c One vial adapter for medicinal product reconstitution
- d One safety injection needle (20G x 1.5")

Follow the instructions below carefully to ensure proper reconstitution of Signifor powder and solvent for suspension for injection before deep intramuscular injection.

Signifor suspension must only be prepared immediately before administration.

Signifor should only be administered by a trained healthcare professional.

Step 1

Remove the Signifor injection kit from refrigerated storage.

ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

Note: If not used within 24 hours, the injection kit can be returned to the fridge.



Step 2

Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.

Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.

Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by a “click”.

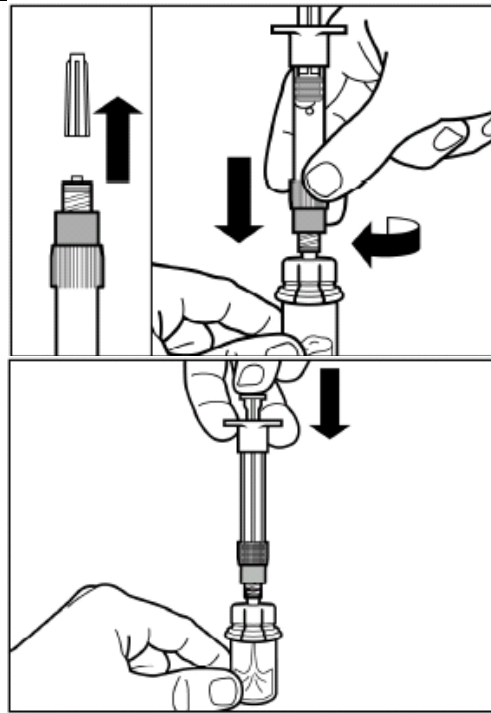
Remove the packaging from the vial adapter by lifting it straight up as shown.



Step 3

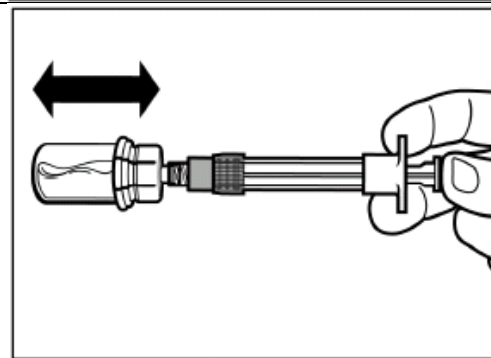
Remove the cap from the syringe pre-filled with solvent and **screw** the syringe onto the vial adapter.

Slowly push the plunger all the way down to transfer all the solvent in the vial.



Step 4

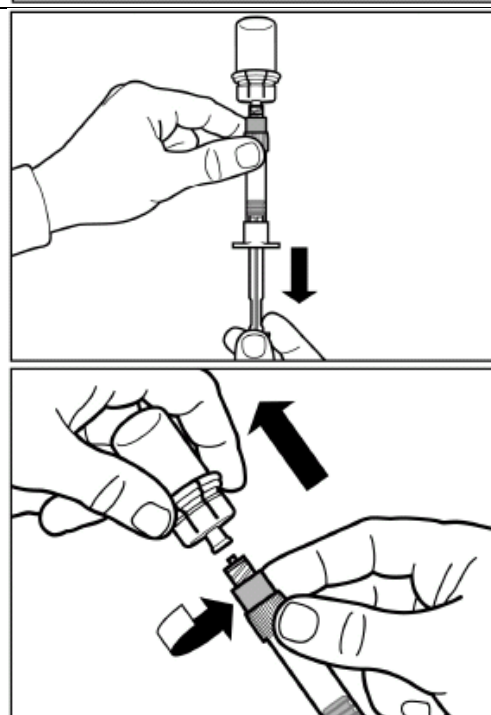
ATTENTION: Keep the plunger pressed and shake the vial **moderately for a minimum of 30 seconds** so that the powder is completely suspended. **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**



Step 5

Turn syringe and vial upside down, **slowly** pull the plunger back and draw the entire content from the vial into the syringe.

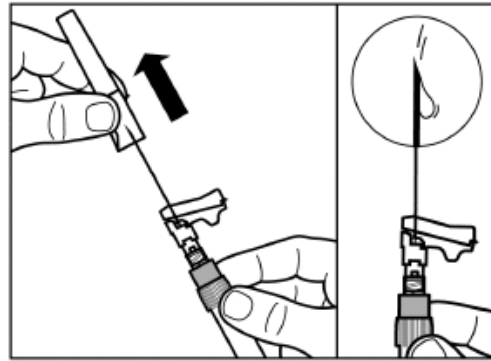
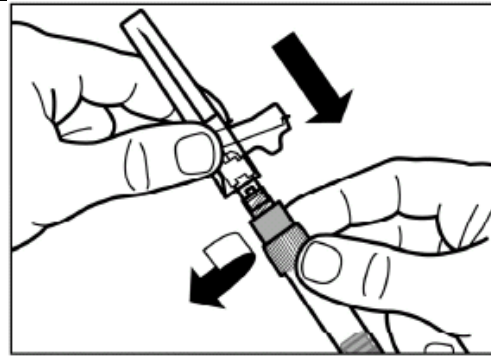
Unscrew the syringe from the vial adapter.



Step 6

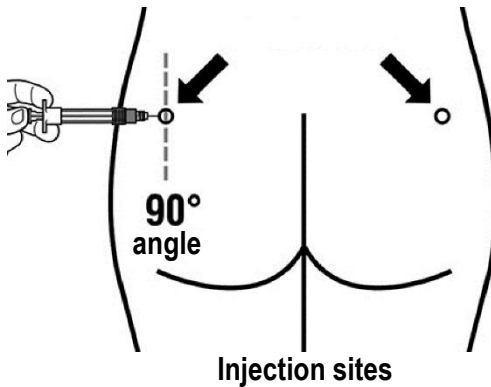
Screw the safety injection needle onto the syringe.

Pull the protective cover straight off the needle. To avoid sedimentation, you may gently shake the syringe to maintain a uniform suspension. Gently tap the syringe to remove any visible bubbles and expel them from the syringe. The reconstituted Signifor is now ready for **immediate** administration.



Step 7

Signifor must be given only by deep intramuscular injection. Prepare the injection site with an alcohol wipe. Insert the needle fully into the left or right gluteus at a 90° angle to the skin. Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated). Slowly depress the plunger until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in Step 8).



Step 8

Activate the safety guard over the needle, in one of the two methods shown:

- either press the hinged section of the safety guard down onto a hard surface (figure A),
- or push the hinge forward with your finger (figure B).

An audible “click” confirms proper activation.

Dispose of syringe immediately in a sharps container.

