1. NAME OF THE MEDICINAL PRODUCT

Signifor 0.3 mg/1ml solution for injection
Signifor 0.6 mg/1ml solution for injection
Signifor 0.9 mg/1ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Signifor 0.3 mg/1ml solution for injection
One ampoule of 1 ml contains 0.3 mg pasireotide (as pasireotide diaspartate).

Signifor 0.6 mg/1ml solution for injection
One ampoule of 1 ml contains 0.6 mg pasireotide (as pasireotide diaspartate).

Signifor 0.9 mg/1ml solution for injection
One ampoule of 1 ml contains 0.9 mg pasireotide (as pasireotide diaspartate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for 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.

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 HbA1c 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 (adrenocorticotropic 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 T_4, 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 (≤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 ≥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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥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 $HbA_{1c} \geq 7\%$ 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

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	hsst1	hsst2	hsst3	hsst4	hsst5
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	>1000	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	>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 IC_{50} 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 ≤2 x ULN and below or equal to their baseline value continued blinded treatment at the randomised dose until month 6. Patients who did not meet these criteria were unblinded and the dose was increased by 0.3 mg twice 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 ≤ULN) after 6 months of treatment and who did not have a dose increase (relative to randomised dose) during this period. Secondary end-points included, among others, changes from baseline in: 24-hour UFC, plasma ACTH, serum cortisol levels, and clinical signs and symptoms of Cushing's disease. All analyses were conducted based on the randomised dose groups.

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

Baseline characteristics were balanced between the two randomised dose groups, except for marked differences in the mean value of baseline 24-hour UFC (1156 nmol/24 h for the 0.6 mg twice 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 ≤1.0 x ULN), partially controlled (UFC >1.0 x ULN but with a reduction in UFC ≥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 % change (n)	Pasireotide 0.9 mg twice daily % 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.

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±8.16% of the radioactivity in faeces and 7.63±2.03% in urine.

Pasireotide demonstrates low clearance (CL/F ~7.6 litres/h for healthy volunteers and ~3.8 litres/h for Cushing's disease patients). Based on the accumulation ratios of AUC, the calculated effective half-life ($t_{1/2,eff}$) in healthy volunteers was approximately 12 hours.

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 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
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

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Do not store above 30°C.
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 30 or 60 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. MANUFACTURER

Novartis Pharma Stein AG, Stein, Switzerland
For Recordati Rare Diseases, Immeuble le Wilson, 70 avenue du Général de Gaulle, 92800 Puteaux, France.

8. REGISTRATION HOLDER

Medison Pharma Ltd., 10 Hashiloach St., POB 7090 Petach Tikva.

9. REGISTRATION NUMBERS

Signifor 0.3 mg/1 ml solution for injection: 150-59-33762
Signifor 0.6 mg/1 ml solution for injection: 150-60-33767
Signifor 0.9 mg/1 ml solution for injection: 150-61-33768

Revised in December 2021