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

Signifor is indicated for the 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, HbA1c 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\textsubscript{1c} [FPG/HbA\textsubscript{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA\textsubscript{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\textsubscript{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).

Cushing’s disease patients with poor glycaemic control (as defined by HbA\textsubscript{1c} values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). In patients with poor glycaemic control, 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**

Bradyarrhythmia 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 bradyarrhythmia, such as history of clinically significant bradyarrhythmia 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 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). 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 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).

Table 1  Adverse reactions in the phase III study in Cushing’s disease patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia, diabetes mellitus</td>
<td>Decreased appetite, type 2 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Sinus bradycardia, QT prolongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea, abdominal pain, nausea</td>
<td>Vomiting, abdominal pain upper</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholelithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Alopecia, pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td>Myalgia, arthralgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction, fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Glycosylated haemoglobin increased</td>
<td>Gamma glutamyltransferase increased, alanine aminotransferase increased, lipase increased, blood glucose increased, blood amylase increased, prothrombin time prolonged</td>
<td></td>
</tr>
</tbody>
</table>

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 HbA1c 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
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 HbA1c 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 HbA1c ≥7% or who were taking antidiabetic medicinal products prior to randomisation tended to have higher mean changes in fasting plasma glucose and HbA1c 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)

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

Results are the mean±SEM of IC\textsubscript{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

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide 0.6 mg twice daily</th>
<th>Pasireotide 0.9 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change (n)</td>
<td>% change (n)</td>
</tr>
<tr>
<td>Mean change in UFC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% from baseline)</td>
<td>Month 6 -27.5* (52)</td>
<td>-48.4 (51)</td>
</tr>
<tr>
<td></td>
<td>Month 12 -41.3 (37)</td>
<td>-54.5 (35)</td>
</tr>
<tr>
<td>Median change in UFC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% from baseline)</td>
<td>Month 6 -47.9 (52)</td>
<td>-47.9 (51)</td>
</tr>
<tr>
<td></td>
<td>Month 12 -67.6 (37)</td>
<td>-62.4 (35)</td>
</tr>
</tbody>
</table>

* 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. $C_{\text{max}}$ 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 ($V_{ss}/F >100$ 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 $\sim$7.6 litres/h for healthy volunteers and $\sim$3.8 litres/h for Cushing’s disease patients). Based on the accumulation ratios of AUC, the calculated effective half-life ($t_{1/2,\text{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\text{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\text{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\text{inf} was increased 60% and 79%, C\text{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\text{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\text{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 \textit{in vitro} and \textit{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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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 20 mg powder and solvent for suspension for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains 20 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

Signifor is indicated for the 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.

4.2 Posology and method of administration

**Posology**

The recommended initial dose 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 by 20 mg decrements.

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). The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks (see section 5.2). The maximum recommended dose for these patients is 40 mg every 4 weeks. 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).

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% (Common Toxicity Criteria 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.

In acromegaly 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 insulinotropic polypeptide [GIP]).
Glycaemic status (fasting plasma glucose/haemoglobin A1c [FPG/HbA1c]) should be assessed prior to starting treatment with pasireotide. FPG/HbA1c monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done 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 HbA1c 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).

Patients with poor glycaemic control (as defined by HbA1c values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). In patients with poor glycaemic control, 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

Bradycairdia 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**

Treatment with Signifor can lead to rapid suppression of ACTH (adrenocorticotropic hormone) secretion. Infrequent cases of hypocortisolism have been reported in clinical studies with pasireotide in acromegaly patients.

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 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). 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 cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T₄, ACTH/cortisol) 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 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**

Safety assessment was made based on 491 acromegaly patients who received pasireotide (419 patients received pasireotide intramuscular use and 72 received pasireotide subcutaneous use) in phase I, II and III studies. The safety profile of pasireotide intramuscular use was consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use.

The most common adverse reactions (incidence ≥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 Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia.
Tabulated list of adverse reactions

Pooled analyses of adverse reactions reported up to the cut-off date of the analysis for studies C2305 and C2402 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).

Table 1   Adverse reactions by preferred term for pasireotide intramuscular use in the two phase III studies in acromegaly patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td>Adrenal insufficiency*</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia, diabetes mellitus</td>
<td>Type 2 diabetes mellitus, glucose tolerance impaired</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Sinus bradycardia**, QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea, abdominal distension, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholelithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Glycosylated haemoglobin increased, alanine aminotransferase increased, blood glucose increased, blood creatine phosphokinase increased</td>
<td>Amylase increased</td>
<td></td>
</tr>
</tbody>
</table>

*  Adrenal insufficiency includes the following preferred terms: adrenal insufficiency and blood cortisol decreased.
**  Sinus bradycardia includes the following preferred terms: bradycardia and sinus bradycardia.
*** Injection site reaction includes the following preferred terms: injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction and injection site swelling.
Description of selected adverse reactions

Glucose metabolism disorders
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 HbA1c >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 HbA1c 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 HbA1c was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

The elevations of fasting plasma glucose and HbA1c 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. 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 all grade 1 or 2 in severity and were comparable between pasireotide intramuscular use and octreotide intramuscular use treated patients. The incidence of such events was highest in the first 3 months of treatment. Injection site reaction-related adverse events were less frequent in inadequately controlled patients compared to medically naïve patients.

QT prolongation
In 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. No patient had a QTcF value >500 ms. 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.

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 with acromegaly 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 hsst.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>hsst1</th>
<th>hsst2</th>
<th>hsst3</th>
<th>hsst4</th>
<th>hsst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>0.93±0.12</td>
<td>0.15±0.02</td>
<td>0.56±0.17</td>
<td>1.5±0.4</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>(SRIF-14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasireotide</td>
<td>9.3±0.1</td>
<td>1.0±0.1</td>
<td>1.5±0.3</td>
<td>&gt;100</td>
<td>0.16±0.01</td>
</tr>
<tr>
<td>Octreotide</td>
<td>280±80</td>
<td>0.38±0.08</td>
<td>7.1±1.4</td>
<td>&gt;1,000</td>
<td>6.3±1.0</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>180±20</td>
<td>0.54±0.08</td>
<td>14±9</td>
<td>230±40</td>
<td>17±5</td>
</tr>
</tbody>
</table>

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 GH in acromegaly.

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 insulinotropic 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.

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 µg/l and sex- and age-adjusted IGF-1 >1.3 × 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 µg/l, 12.1 µg/l and 9.5 µg/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 x ULN, respectively.
The primary efficacy endpoint was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 μg/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)

<table>
<thead>
<tr>
<th></th>
<th>Signifor intramuscular use 40 mg N=65</th>
<th>Signifor intramuscular use 60 mg N=65</th>
<th>Active control N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH&lt;2.5 μg/l and normalised</td>
<td>n (%), p value</td>
<td>n (%), p value</td>
<td>n (%)</td>
</tr>
<tr>
<td>IGF-1*</td>
<td>10 (15.4%), p=0.0006</td>
<td>13 (20.0%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normalisation of IGF-1</td>
<td>16 (24.6%), p&lt;0.0001</td>
<td>17 (26.2%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GH&lt;2.5 μg/l</td>
<td>23 (35.4%)</td>
<td>28 (43.1%)</td>
<td>9 (13.2%)</td>
</tr>
</tbody>
</table>

* 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.

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 µg/l and/or IGF-1 > 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 µg/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

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide intramuscular use</th>
<th>Octreotide intramuscular use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) N=176</td>
<td>n (%) N=182</td>
<td></td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l and normalised IGF-1*</td>
<td>31.3%</td>
<td>19.2%</td>
<td>p=0.007</td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l and IGF-1 &lt; ULN</td>
<td>35.8%</td>
<td>20.9%</td>
<td>-</td>
</tr>
<tr>
<td>Normalised IGF-1</td>
<td>38.6%</td>
<td>23.6%</td>
<td>p=0.002</td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l</td>
<td>48.3%</td>
<td>51.6%</td>
<td>p=0.536</td>
</tr>
</tbody>
</table>

* 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 µg/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%).

**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 (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

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

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 20 mg to 60 mg every 4 weeks in patients with acromegaly.

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 with acromegaly.

Demographics
Population pharmacokinetic (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 20 mg pasireotide. Solvent: colourless pre-filled syringe (glass) with front and plunger stopper (chlorobutyl rubber), containing 2 ml solvent.

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).

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 finger
   An 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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/013

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 40 mg powder and solvent for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 40 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

Signifor is indicated for the 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.

4.2 Posology and method of administration

Posology

The recommended initial dose 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 by 20 mg decrements.

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). The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks (see section 5.2). The maximum recommended dose for these patients is 40 mg every 4 weeks. 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).

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% (Common Toxicity Criteria 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.

In acromegaly 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 insulinotropic polypeptide [GIP]).
Glycaemic status (fasting plasma glucose/haemoglobin A1c [FPG/HbA1c]) should be assessed prior to starting treatment with pasireotide. FPG/HbA1c monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done 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 HbA1c 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).

Patients with poor glycaemic control (as defined by HbA1c values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). In patients with poor glycaemic control, 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**

Treatment with Signifor can lead to rapid suppression of ACTH (adrenocorticotropic hormone) secretion. Infrequent cases of hypocortisolism have been reported in clinical studies with pasireotide in acromegaly patients.

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 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). 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 cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T4, ACTH/cortisol) 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 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

Safety assessment was made based on 491 acromegaly patients who received pasireotide (419 patients received pasireotide intramuscular use and 72 received pasireotide subcutaneous use) in phase I, II and III studies. The safety profile of pasireotide intramuscular use was consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use.

The most common adverse reactions (incidence ≥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 Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia.
Tabulated list of adverse reactions

Pooled analyses of adverse reactions reported up to the cut-off date of the analysis for studies C2305 and C2402 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).

Table 1  Adverse reactions by preferred term for pasireotide intramuscular use in the two phase III studies in acromegaly patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td>Adrenal insufficiency*</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia, diabetes mellitus</td>
<td>Type 2 diabetes mellitus, glucose tolerance impaired</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Sinus bradycardia**, QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea, abdominal distension, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholelithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Glycosylated haemoglobin increased, alanine aminotransferase increased, blood glucose increased, blood creatine phosphokinase increased</td>
<td>Amylase increased</td>
<td></td>
</tr>
</tbody>
</table>

* Adrenal insufficiency includes the following preferred terms: adrenal insufficiency and blood cortisol decreased.

** Sinus bradycardia includes the following preferred terms: bradycardia and sinus bradycardia.

*** Injection site reaction includes the following preferred terms: injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction and injection site swelling.
Description of selected adverse reactions

Glucose metabolism disorders
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 HbA1c >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 HbA1c 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 HbA1c was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

The elevations of fasting plasma glucose and HbA1c 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. 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 all grade 1 or 2 in severity and were comparable between pasireotide intramuscular use and octreotide intramuscular use treated patients. The incidence of such events was highest in the first 3 months of treatment. Injection site reaction-related adverse events were less frequent in inadequately controlled patients compared to medically naïve patients.

QT prolongation
In 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. No patient had a QTcF value >500 ms. 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.

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 with acromegaly 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)

<table>
<thead>
<tr>
<th>Compound</th>
<th>hsst1</th>
<th>hsst2</th>
<th>hsst3</th>
<th>hsst4</th>
<th>hsst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin (SRIF-14)</td>
<td>0.93±0.12</td>
<td>0.15±0.02</td>
<td>0.56±0.17</td>
<td>1.5±0.4</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>9.3±0.1</td>
<td>1.0±0.1</td>
<td>1.5±0.3</td>
<td>&gt;100</td>
<td>0.16±0.01</td>
</tr>
<tr>
<td>Octreotide</td>
<td>280±80</td>
<td>0.38±0.08</td>
<td>7.1±1.4</td>
<td>&gt;1,000</td>
<td>6.3±1.0</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>180±20</td>
<td>0.54±0.08</td>
<td>14±9</td>
<td>230±40</td>
<td>17±5</td>
</tr>
</tbody>
</table>

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 GH in acromegaly.

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 insulino tropic 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.

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 μg/l and sex- and age-adjusted IGF-1 >1.3 × 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 μg/l, 12.1 μg/l and 9.5 μg/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 x ULN, respectively.

The primary efficacy endpoint was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 μg/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)

<table>
<thead>
<tr>
<th></th>
<th>Signifor intramuscular use</th>
<th>Signifor intramuscular use</th>
<th>Active control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 mg</td>
<td>60 mg</td>
<td>N=68</td>
</tr>
<tr>
<td></td>
<td>N=65</td>
<td>N=65</td>
<td>n (%)</td>
</tr>
<tr>
<td>GH&lt;2.5 µg/l and normalised IGF-1*</td>
<td>10 (15.4%), p=0.0006</td>
<td>13 (20.0%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normalisation of IGF-1</td>
<td>16 (24.6%), p&lt;0.0001</td>
<td>17 (26.2%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GH&lt;2.5 µg/l</td>
<td>23 (35.4%)</td>
<td>28 (43.1%)</td>
<td>9 (13.2%)</td>
</tr>
</tbody>
</table>

* 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 40 mg 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.

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 µg/l and/or IGF-1 >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 μg/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

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide intramuscular use</th>
<th>Octreotide intramuscular use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH &lt;2.5 μg/l and normalised IGF-1*</td>
<td>31.3%</td>
<td>19.2%</td>
<td>0.007</td>
</tr>
<tr>
<td>GH &lt;2.5 μg/l and IGF-1 ≤ULN</td>
<td>35.8%</td>
<td>20.9%</td>
<td>-</td>
</tr>
<tr>
<td>Normalised IGF-1</td>
<td>38.6%</td>
<td>23.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>GH &lt;2.5 μg/l</td>
<td>48.3%</td>
<td>51.6%</td>
<td>0.536</td>
</tr>
</tbody>
</table>

* 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 μg/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%).

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 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Distribution
In healthy volunteers, pasireotide intramuscular use is widely distributed with large apparent volume of distribution \((V/F >100 \text{ litres})\). 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 \textit{in vitro} data pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein). Based on \textit{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 \textit{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.

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 20 mg to 60 mg every 4 weeks in patients with acromegaly.

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 with acromegaly.

Demographics
Population pharmacokinetic (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 40 mg pasireotide. Solvent: colourless pre-filled syringe (glass) with front and plunger stopper (chlorobutyl rubber), containing 2 ml solvent.
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).

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 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 finger
   An 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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/014
EU/1/12/753/015

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 60 mg powder and solvent for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Signifor is indicated for the 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.

4.2 Posology and method of administration

Posology

The recommended initial dose 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 by 20 mg decrements.

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). The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 20 mg every 4 weeks (see section 5.2). The maximum recommended dose for these patients is 40 mg every 4 weeks. 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).

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% (Common Toxicity Criteria 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.

In acromegaly 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 insulinotropic polypeptide [GIP]).
Glycaemic status (fasting plasma glucose/haemoglobin A\textsubscript{1c} [FPG/HbA\textsubscript{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA\textsubscript{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\textsubscript{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).

Patients with poor glycaemic control (as defined by HbA\textsubscript{1c} values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycaemia and associated complications (e.g. ketoacidosis). In patients with poor glycaemic control, 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**

Treatment with Signifor can lead to rapid suppression of ACTH (adrenocorticotropic hormone) secretion. Infrequent cases of hypocortisolism have been reported in clinical studies with pasireotide in acromegaly patients.

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 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). 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 cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T₄, ACTH/cortisol) 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 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, pimozone, haloperidol, tiapride, amisulpride, sertindole, methodone), 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**

Safety assessment was made based on 491 acromegaly patients who received pasireotide (419 patients received pasireotide intramuscular use and 72 received pasireotide subcutaneous use) in phase I, II and III studies. The safety profile of pasireotide intramuscular use was consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use.

The most common adverse reactions (incidence ≥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 Grade 3 and 4 adverse reactions were mostly related to hyperglycaemia.
Tabulated list of adverse reactions

Pooled analyses of adverse reactions reported up to the cut-off date of the analysis for studies C2305 and C2402 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).

Table 1  Adverse reactions by preferred term for pasireotide intramuscular use in the two phase III studies in acromegaly patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Adrenal insufficiency*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia, diabetes mellitus</td>
<td>Type 2 diabetes mellitus, glucose tolerance impaired</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia**</td>
<td></td>
<td>Sinus bradycardia**, QT prolongation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea, abdominal distension, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholelithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Glycosylated haemoglobin increased, alanine aminotransferase increased, blood glucose increased, blood creatine phosphokinase increased</td>
<td>Amylase increased</td>
<td></td>
</tr>
</tbody>
</table>

* Adrenal insufficiency includes the following preferred terms: adrenal insufficiency and blood cortisol decreased.
** Sinus bradycardia includes the following preferred terms: bradycardia and sinus bradycardia.
*** Injection site reaction includes the following preferred terms: injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction and injection site swelling.
Description of selected adverse reactions

Glucose metabolism disorders
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 HbA1c >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 HbA1c 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 HbA1c was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

The elevations of fasting plasma glucose and HbA1c 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. 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 all grade 1 or 2 in severity and were comparable between pasireotide intramuscular use and octreotide intramuscular use treated patients. The incidence of such events was highest in the first 3 months of treatment. Injection site reaction-related adverse events were less frequent in inadequately controlled patients compared to medically naïve patients.

QT prolongation
In 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. No patient had a QTcF value >500 ms. 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.

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 with acromegaly 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)

<table>
<thead>
<tr>
<th>Compound</th>
<th>hsst1</th>
<th>hsst2</th>
<th>hsst3</th>
<th>hsst4</th>
<th>hsst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin (SRIF-14)</td>
<td>0.93±0.12</td>
<td>0.15±0.02</td>
<td>0.56±0.17</td>
<td>1.5±0.4</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>9.3±0.1</td>
<td>1.0±0.1</td>
<td>1.5±0.3</td>
<td>&gt;100</td>
<td>0.16±0.01</td>
</tr>
<tr>
<td>Octreotide</td>
<td>280±80</td>
<td>0.38±0.08</td>
<td>7.1±1.4</td>
<td>&gt;1,000</td>
<td>6.3±1.0</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>180±20</td>
<td>0.54±0.08</td>
<td>14±9</td>
<td>230±40</td>
<td>17±5</td>
</tr>
</tbody>
</table>

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 GH in acromegaly.

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 insulinotropic 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.

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 μg/l and sex- and age-adjusted IGF-1 >1.3 × 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 μg/l, 12.1 μg/l and 9.5 μg/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 x ULN, respectively.
The primary efficacy endpoint was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 μg/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)**

<table>
<thead>
<tr>
<th></th>
<th>Signifor intramuscular use</th>
<th>Signifor intramuscular use</th>
<th>Active control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 mg</td>
<td>60 mg</td>
<td>N=68 n (%)</td>
</tr>
<tr>
<td>GH&lt;2.5 μg/l and normalised</td>
<td>10 (15.4%), p=0.0006</td>
<td>13 (20.0%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IGF-1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalisation of IGF-1</td>
<td>16 (24.6%), p&lt;0.0001</td>
<td>17 (26.2%), p&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GH&lt;2.5 μg/l</td>
<td>23 (35.4%)</td>
<td>28 (43.1%)</td>
<td>9 (13.2%)</td>
</tr>
</tbody>
</table>

* 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.

**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 µg/l and/or IGF-1 >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 µg/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

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide intramuscular use</th>
<th>Octreotide intramuscular use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l and normalised IGF-1*</td>
<td>31.3%</td>
<td>19.2%</td>
<td>p=0.007</td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l and IGF-1 &lt;ULN</td>
<td>35.8%</td>
<td>20.9%</td>
<td>-</td>
</tr>
<tr>
<td>Normalised IGF-1</td>
<td>38.6%</td>
<td>23.6%</td>
<td>p=0.002</td>
</tr>
<tr>
<td>GH &lt;2.5 µg/l</td>
<td>48.3%</td>
<td>51.6%</td>
<td>p=0.536</td>
</tr>
</tbody>
</table>

* 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 µg/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%).

**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 (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

**Absorption**

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

**Distribution**

In healthy volunteers, pasireotide intramuscular use is widely distributed with large apparent volume of distribution (V<sub>z</sub>/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.

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 20 mg to 60 mg every 4 weeks in patients with acromegaly.

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\(_{\text{inf,u}}\)) 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\(_{\text{inf}}\) was increased 60% and 79%, C\(_{\text{max}}\) 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 with acromegaly.

Demographics
Population pharmacokinetic (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 60 mg pasireotide. Solvent: colourless pre filled syringe (glass) with front and plunger stopper (chlorobutyl rubber), containing 2 ml solvent.

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).

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 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 finger
   An 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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/016
EU/1/12/753/017

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 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

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 diaspartate).

**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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORIZATION 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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Quantity</th>
<th>Details</th>
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<tbody>
<tr>
<td>EU/1/12/753/002</td>
<td>18</td>
<td>18 ampoules (3x6)</td>
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<td>EU/1/12/753/003</td>
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<td>EU/1/12/753/004</td>
<td>60</td>
<td>60 ampoules (10x6)</td>
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</tbody>
</table>

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 diaspartate).

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

Signifor 0.3 mg

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

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<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<td>pasireotide</td>
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<td>SC</td>
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| 2. METHOD OF ADMINISTRATION                                   |

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<th>3. EXPIRY DATE</th>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<th>6. OTHER</th>
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</thead>
</table>
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 diaspartate).

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**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

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 diaspartate).

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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Quantity</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/12/753/006</td>
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<td>3x6</td>
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<td>EU/1/12/753/007</td>
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<td>5x6</td>
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<td>EU/1/12/753/008</td>
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<td>10x6</td>
</tr>
</tbody>
</table>

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 diaspartate).

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

Signifor 0.6 mg

16. INFORMATION IN BRAILLE

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
<table>
<thead>
<tr>
<th>Section</th>
<th>Information</th>
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<tbody>
<tr>
<td>9.</td>
<td>SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
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<td>Store in the original package in order to protect from light.</td>
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<tr>
<td>10.</td>
<td>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>Novartis Europharm Limited</td>
</tr>
<tr>
<td></td>
<td>Frimley Business Park</td>
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<td></td>
<td>Camberley GU16 7SR</td>
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<tr>
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<td>13.</td>
<td>BATCH NUMBER</td>
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<td></td>
<td>Lot</td>
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<tr>
<td>14.</td>
<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td>15.</td>
<td>INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td>16.</td>
<td>INFORMATION IN BRAILLE</td>
</tr>
<tr>
<td></td>
<td>Signifor 0.9 mg</td>
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<tr>
<td>17.</td>
<td>UNIQUE IDENTIFIER – 2D BARCODE</td>
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<td></td>
<td>2D barcode carrying the unique identifier included.</td>
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<td>UNIQUE IDENTIFIER - HUMAN READABLE DATA</td>
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<td>PC:</td>
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<td>SN:</td>
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<td></td>
<td>NN:</td>
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</table>
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 diaspartate).

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**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

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<thead>
<tr>
<th>Number</th>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>EU/1/12/753/010</td>
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<tr>
<td>EU/1/12/753/011</td>
<td>30</td>
<td>ampoules (5x6)</td>
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<tr>
<td>EU/1/12/753/012</td>
<td>60</td>
<td>ampoules (10x6)</td>
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</table>

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)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signifor 0.9 mg solution for injection</td>
</tr>
<tr>
<td>pasireotide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml solution for injection contains 0.9 mg pasireotide (as pasireotide diaspaptate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also contains: Mannitol, tartaric acid, sodium hydroxide, water for injections. See package leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection</td>
</tr>
<tr>
<td>Multipack: 18 (3 packs of 6) ampoules.</td>
</tr>
<tr>
<td>Multipack: 30 (5 packs of 6) ampoules.</td>
</tr>
<tr>
<td>Multipack: 60 (10 packs of 6) ampoules.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Subcutaneous use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
<tr>
<th>Marketing Authorisation Number</th>
<th>Description</th>
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<tr>
<td>EU/1/12/753/010</td>
<td>18 ampoules (3x6)</td>
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<tr>
<td>EU/1/12/753/011</td>
<td>30 ampoules (5x6)</td>
</tr>
<tr>
<td>EU/1/12/753/012</td>
<td>60 ampoules (10x6)</td>
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</table>

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 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:
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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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 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:
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

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/753/014

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

### 15. INSTRUCTIONS ON USE

Signifor 40 mg

### 16. INFORMATION IN BRAILLE

### 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:

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 AUTHORITY

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORIZATION 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:
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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

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<thead>
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<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Signifor 40 mg powder for injection</td>
</tr>
<tr>
<td>pasireotide</td>
</tr>
<tr>
<td>IM</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<table>
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<th>3. EXPIRY DATE</th>
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**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PRE-FILLED SYRINGE LABEL**

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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:
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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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:
### 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:
- 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**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

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:
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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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** |

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<th>6. OTHER</th>
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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 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 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.

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**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.
  - Gallstones. You may experience 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.
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
- 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)

**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 diaspartate).
  - Signifor 0.6 mg: One ampoule of 1 ml solution contains 0.6 mg pasireotide (as pasireotide diaspartate).
  - Signifor 0.9 mg: One ampoule of 1 ml solution contains 0.9 mg pasireotide (as pasireotide diaspartate).
- 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**
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

**Manufacturer**
Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>Novartis Pharma N.V.  Tel: +32 2 246 16 11</td>
</tr>
<tr>
<td>България</td>
<td>Novartis Pharma Services Inc. Tел.: +359 2 489 98 28</td>
</tr>
<tr>
<td>Česká republika</td>
<td>Novartis s.r.o. Tel: +420 225 775 111</td>
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<tr>
<td>Danmark</td>
<td>Novartis Healthcare A/S Tlf: +45 39 16 84 00</td>
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<tr>
<td>Deutschland</td>
<td>Novartis Pharma GmbH Tel: +49 911 273 0</td>
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<tr>
<td>Eesti</td>
<td>Novartis Pharma Services Inc. Tel: +372 66 30 810</td>
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<tr>
<td>Ελλάδα</td>
<td>Novartis (Hellas) A.E.B.E. Τηλ: +30 210 281 17 12</td>
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<td>Österreich</td>
<td>Novartis Pharma GmbH Tel: +43 1 86 6570</td>
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</table>
España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

Polska
Novartis Poland Sp. z o.o.
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Novartis Pharma S.A.S.
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United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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.
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.

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.

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 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, quindine, 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**
The recommended dose of Signifor 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 may need to be changed. The dose given in each injection can be reduced to 20 mg or, if the treatment is not fully effective, your doctor can increase the dose to 60 mg.

If you have liver disease before you start Signifor treatment, your doctor may want to start your treatment with a dose of 20 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.
- Gallstones. You may experience 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).

**Other side effects of Signifor may include:**

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

**Common (may affect up to 1 in 10 people)**
- Abdominal pain
- Tiredness, fatigue, pale skin (signs of low level of red blood cells)
- Headache
- Bloating
- Nausea
- 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, alanine aminotransferase in the blood)
- Hair loss
Uncommon (may affect up to 1 in 100 people)
- Change in pancreatic function blood test results (amylase)

**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 20 mg: each vial contains 20 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 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 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 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
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
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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.

<table>
<thead>
<tr>
<th>ATTENTION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are two critical steps in the reconstitution of Signifor. <strong>Not following them could result in failure to deliver the injection appropriately.</strong></td>
</tr>
<tr>
<td>• <strong>The injection kit must reach room temperature.</strong> 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.</td>
</tr>
<tr>
<td>• After adding the solvent, <strong>shake the vial moderately</strong> for a minimum of 30 seconds <strong>until a uniform suspension is formed.</strong></td>
</tr>
</tbody>
</table>

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.

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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.