SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Signifor 60 mg powder and solvent for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Signifor 60 mg powder and solvent for suspension for injection

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

Powder: slightly yellowish to yellowish powder.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

4.2 Posology and method of administration

Posology

Acromegaly

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

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

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

Cushing's disease

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

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

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

Switch from subcutaneous to intramuscular formulation in Cushing's disease

There are no clinical data available on switching from the subcutaneous to the intramuscular pasireotide formulation. If such a switch should be required, the recommended initial dose for the treatment of Cushing's disease is 10 mg of

pasireotide by deep intramuscular injection every 4 weeks. The patient should be monitored for response and tolerability and further dose adjustments may be needed.

Missed dose

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

Special populations

Elderly patients (≥65 years)

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

Renal impairment

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

Hepatic impairment

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

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

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

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

Paediatric population

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

Method of administration

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

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

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

4.3 Contraindications

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

Severe hepatic impairment (Child Pugh C).

4.4 Special warnings and precautions for use

Glucose metabolism

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

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

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

Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done weekly for the first three months and

periodically thereafter, as clinically appropriate, as well as over the first four to six weeks after any dose increase. In addition, monitoring of FPG 4 weeks and HbA_{1c} 3 months after the end of the treatment should be performed.

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

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

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

Liver tests

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

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

Cardiovascular related events

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

medicinal products to control electrolyte balance, may be necessary (see also section 4.5).

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

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

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

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

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

Hypocortisolism

The suppression of ACTH (adrenocorticotropic hormone) secretion can result in hypocortisolism in patients treated with Signifor. It is therefore necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyperkalaemia, hyponatraemia, hypoglycaemia). In the event of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of Signifor therapy may be necessary. Rapid decreases in cortisol levels may be associated with decreases in white blood cell count.

Gallbladder and related events

Cholelithiasis (gallstones) is a recognised adverse reaction associated with somatostatin analogues and has frequently been reported in clinical studies with

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

Pituitary hormones

As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones other than GH and/or IGF-1 in patients with acromegaly and ACTH/cortisol in patients with Cushing's disease cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T_4) before and periodically during Signifor therapy should therefore be considered, as clinically appropriate.

Effect on female fertility

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

Coagulation abnormalities

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

Renal impairment

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

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Anticipated pharmacokinetic interactions resulting in effects on pasireotide

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

Anticipated pharmacokinetic interactions resulting in effects on other medicinal products

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

Anticipated pharmacodynamic interactions

Medicinal products that prolong the QT interval

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

Bradycardic medicinal products

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

Insulin and antidiabetic medicinal products

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Signifor may have a minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue, dizziness or headache during treatment with Signifor.

4.8 Undesirable effects

Summary of the safety profile

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

Acromegaly

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

Cushing's disease

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

Tabulated list of adverse reactions

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

Table 1 Adverse reactions by preferred term for pasireotide intramuscular use

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders		Anaemia		
Endocrine disorders		Adrenal insufficiency*		
Metabolism and nutrition disorders	Hyperglycaemia, diabetes mellitus	Type 2 diabetes mellitus, glucose tolerance impaired, decreased appetite		Diabetic ketoacidosis
Nervous system disorders		Headache, dizziness		
Cardiac disorders		Sinus bradycardia*, QT prolongation		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain*	Abdominal distension, vomiting		Steatorrhea Faeces discoloured

Hepatobiliary disorders	Cholelithiasis	Cholecystitis*, cholestasis		
Skin and subcutaneous tissue disorders		Alopecia, pruritus		
General disorders and administration site conditions	Fatigue*	Injection site reaction*		
Investigations		Glycosylated haemoglobin increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood glucose increased, blood creatine phosphokinase increased, lipase increased	Amylase increased, prothrombin time prolonged	

* Grouped terms: Adrenal insufficiency includes adrenal insufficiency and blood cortisol decreased. Sinus bradycardia includes bradycardia and sinus bradycardia. Abdominal pain includes abdominal pain and abdominal pain upper. Injection site reaction includes injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction, injection site hypersensitivity and injection site swelling. Cholecystitis includes cholecystitis acute and cholecystitis chronic. Fatigue includes fatigue and asthenia.

Description of selected adverse reactions

Glucose metabolism disorders

Acromegaly

In acromegaly patients elevated fasting glucose level was the most frequently reported grade 3/4 laboratory abnormality in the two phase III studies. In study C2305, grade 3 elevated fasting glucose levels were reported in 9.7% and 0.6% and grade 4 in 0.6% and 0% of acromegaly patients treated with pasireotide intramuscular use and octreotide intramuscular use, respectively. In study C2402, grade 3 elevated fasting glucose levels were reported in 14.3% and 17.7% of acromegaly patients treated with pasireotide intramuscular use 40 mg and 60 mg respectively, and in no patients in the active control group. Two cases of hyperglycaemiarelated 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 HbA_{1c} levels peaked within the first three months of treatment with pasireotide intramuscular use. In medically naïve patients (study C2305), the mean absolute increase in FPG and HbA_{1c} was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

The degree and frequency of hyperglycaemia observed in the two pivotal studies in acromegaly patients were higher with Signifor intramuscular use than with active control

(octreotide intramuscular use or lanreotide deep subcutaneous injection). In a pooled analysis of the two pivotal studies, the overall incidence of hyperglycaemiarelated adverse reactions was 58.6% (all grades) and 9.9% (CTC Grade 3 and 4) for Signifor intramuscular use versus 18.0% (all grades) and 1.1% (CTC Grade 3 and 4) for the active control. In the pivotal study with patients inadequately controlled on another somatostatin analogue, the proportion of patients not previously treated with antidiabetic agents who required commencement of antidiabetic 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 antidiabetic therapy during the study was 36% in the Signifor arm compared to 4.4% in the active control arm.

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

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

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

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

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

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

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

Results are the mean±SEM of 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 and ACTH in Cushing's disease.

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

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

Glucose metabolism

In a randomised double-blinded mechanism study conducted in healthy volunteers, the development of hyperglycaemia with pasireotide administered as pasireotide subcutaneous use at doses of 0.6 and 0.9 mg twice a day was related to significant decreases in insulin secretion as well as incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent 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 in acromegaly patients and in one phase III, multicentre study in Cushing's disease patients.

Acromegaly study C2402, inadequately controlled patients

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

Inadequately controlled patients in study C2402 are defined as patients with a mean GH concentration of a 5-point profile over a 2-hour period >2.5 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)

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

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

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

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

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

Acromegaly study C2305 patients who had no prior medical treatment

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

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

The starting dose was 40 mg for pasireotide intramuscular use and 20 mg for octreotide intramuscular use. Dose increase for efficacy was allowed at the discretion of the investigators after three and six months of treatment if biochemical parameters showed a mean GH ≥2.5 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

	Pasireotide intramuscular use n (%) N=176	**Octreotide intramuscular use n (%) N=182**	**p-value**
GH <2.5 µg/l and normalised IGF-1*	31.3%	19.2%	p=0.007
GH <2.5 µg/l and IGF-1 ≤ULN	35.8%	20.9%	-
Normalised IGF-1	38.6%	23.6%	p=0.002
GH <2.5 µg/l	48.3%	51.6%	p=0.536

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

ULN = upper limit of normal

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

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

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

Extension phase

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

During the extension phase, 74 patients continued receiving pasireotide intramuscular use and 46 patients continued with octreotide intramuscular use treatment. At month 25, 48.6% of patients (36/74) in the pasireotide intramuscular use group and 45.7% (21/46) in the octreotide intramuscular use group achieved biochemical control. The percentage of patients who had mean GH values <2.5 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%).

Cushing's disease study G2304

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

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

Results

The study met the primary efficacy objective for both dose groups (lower bound of the 95% CI for the response rate of each treatment arm >15%). At month 7, a mUFC

response was achieved in 41.9% and 40.8% of patients randomised to starting doses of 10 mg and 30 mg, respectively. The proportion of patients who either attained mUFC ≤ULN or a mUFC reduction from baseline of at least 50% was 50.0% in the 10 mg dose group and 56.6% in the 30 mg dose groups (Table 5).

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

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

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

* Primary endpoint using LOCF (last observation carried forward)

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

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

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

In healthy volunteers, pasireotide intramuscular use is widely distributed with large apparent volume of distribution (V_z/F >100 litres). Distribution between blood cells and plasma is concentration independent and shows that pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

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

Biotransformation

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

Elimination

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

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

Linearity and time dependency

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

Special populations

Paediatric population

No studies have been performed in paediatric patients.

Patients with renal impairment

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

Patients with hepatic impairment

No clinical studies in subjects with liver impairment have been performed with pasireotide intramuscular use. In a clinical study of a single subcutaneous dose of pasireotide in subjects with impaired hepatic function, statistically significant differences were found in subjects with moderate and severe hepatic impairment (Child-Pugh B and C). In subjects with moderate and severe hepatic impairment,

AUC_{inf} was increased 60% and 79%, C_{max} was increased 67% and 69%, and CL/F was decreased 37% and 44%, respectively.

Elderly patients (≥65 years)

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

Demographics

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

5.3 Preclinical safety data

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

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

Solvent

Carmellose sodium
Mannitol
Poloxamer 188
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

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

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

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

Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

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

Recordati Rare Diseases
Tour Hekla
52 avenue du Général de Gaulle
92800 Puteaux
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15266/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

06/02/2025