

Signifor® LAR

DESCRIPTION AND COMPOSITION

Signifor LAR is a long-acting depot injection form of pasireotide, powder for suspension for injection to be suspended in a solvent immediately prior to i.m. injection.

Pharmaceutical form(s)

Powder and solvent for suspension for injection

Powder: Slightly yellowish to yellowish powder in vial

Solvent for suspension for injection: clear, colorless to slightly yellow to slightly brown solution in pre-filled syringe

Active substance(s)

Each vial contains:

Signifor LAR 20 mg – 20 mg pasireotide (as pamoate)

Signifor LAR 40 mg - 40 mg pasireotide (as pamoate)

Signifor LAR 60 mg - 60 mg pasireotide (as pamoate)

Excipients

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

Pre-filled syringe: Carmellose sodium, mannitol, poloxamer 188, water for injections.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Signifor LAR 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.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

The recommended initial dose of Signifor LAR is 40 mg administered by deep intramuscular injection every 4 weeks (q28d).

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

Management of suspected adverse reactions or over response to treatment (IGF-1 < lower limit of normal) may require dose reduction of Signifor LAR. The dose may be decreased, either temporarily or permanently, by 20 mg decrements.

If a dose of Signifor LAR is missed, the injection should be administered as soon as possible and the next injection dose should be planned 4 weeks thereafter to resume normal schedule every 4 weeks.

Special populations

Renal impairment

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

Hepatic impairment

Dose adjustment is not required in patients with mildly impaired hepatic function (Child-Pugh A). For patients with moderately impaired hepatic function (Child-Pugh B) the recommended initial dose is 20 mg every 4 weeks and the maximum recommended dose is 40 mg every 4 weeks (see section CLINICAL PHARMACOLOGY). Signifor LAR should not be used in patients with severe hepatic impairment (Child Pugh C) (see section CONTRAINDICATIONS).

Pediatric patients

Signifor LAR is not recommended for use in pediatric patients with acromegaly as there are no clinical data available in patients under 18 years of age.

Geriatric patients (65 years of age or older)

There are limited data on the use of Signifor LAR in patients older than 65 years but there is no evidence suggesting that a dose adjustment is required in elderly patients (see section CLINICAL PHARMACOLOGY).

Method of administration

Signifor LAR should only be administered by deep intramuscular injection by a trained health care professional. Signifor LAR suspension must only be prepared immediately before administration. The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle (see section INSTRUCTIONS FOR USE).

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh C).

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Glucose metabolism

Alterations in blood glucose levels have been seen in healthy volunteers and patients treated with pasireotide. Hyperglycemia and less frequently hypoglycemia, were observed in subjects participating in clinical trials with pasireotide (see section ADVERSE DRUGS REACTIONS).

The development of hyperglycemia appears to be related to decrease in secretion of insulin as well as incretin hormones (i.e. Glucagon-like peptide-1 [GLP-1] and glucose-dependent insulintropic polypeptide [GIP]) (see section CLINICAL PHARMACOLOGY). In acromegaly patients who developed hyperglycemia, the condition generally appeared to respond to antidiabetic therapy. Dose reductions or discontinuation of treatment with pasireotide due to hyperglycemia were infrequent in clinical studies with pasireotide.

Glycemic status (fasting plasma glucose/hemoglobin 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. After treatment discontinuation, glycemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

If hyperglycemia develops in a patient treated with Signifor LAR, the initiation or adjustment of anti-diabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycemia. If uncontrolled hyperglycemia persists despite appropriate medical management the dose of Signifor LAR should be reduced or the treatment discontinued. There have been post-marketing cases of ketoacidosis with Signifor LAR in patients with and without a history of diabetes. In some cases, factors predisposing to ketoacidosis such as acute illness, infection, pancreatic disorders (e.g. pancreatic malignancy or pancreatic surgery), and alcohol abuse were present. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of diabetes history.

In patients with poor glycemic control (as defined by HbA1c values > 8% while receiving anti-diabetic therapy), diabetes management and monitoring should be intensified prior to initiation and during Signifor LAR therapy.

Cardiovascular related events

Bradycardia has been reported with the use of pasireotide (see section ADVERSE DRUG REACTIONS). 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, should be carefully monitored. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control electrolyte balance, may be necessary.

Pasireotide has been shown to prolong the QT interval in healthy subjects based on two studies conducted with the s.c. formulation. Additional analysis of thorough QT study data, indicating quantitative ECG beat to beat restitution, showed that pasireotide does not alter cardiac repolarization in the same manner as drugs known to prolong QT that have been associated with pro-arrhythmia (see section CLINICAL PHARMACOLOGY). The Phase III studies in acromegaly patients did not identify any clinically meaningful differences in QT prolongation events between Signifor LAR 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 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 anti-arrhythmic medicinal products or other substances that are known to lead to QT prolongation;
- with hypokalemia and/or hypomagnesemia.

A baseline ECG is recommended prior to initiating therapy with Signifor LAR. Monitoring for an effect on the QTc interval is advisable 21 days after initiating therapy and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to Signifor LAR administration and should be monitored periodically during therapy.

Liver tests

Mild transient elevations in aminotransferases are commonly observed in patients treated with pasireotide. A few cases of concurrent elevations in ALT (alanine aminotransferase) greater than 3 x ULN (upper limit normal) and bilirubin greater than 2 x ULN have also been observed (see section ADVERSE DRUG REACTIONS).

Monitoring of liver function is recommended prior to treatment with Signifor LAR, and after the first 2 to 3 weeks, then monthly for 3 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 Signifor LAR should be discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver impairment, 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 Signifor LAR, patients should be monitored until resolution. Treatment should not be restarted if the liver function abnormalities are suspected to be related to Signifor LAR.

Gallbladder and related events

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

Pituitary hormones

Deficiency of pituitary secreted hormones is common after trans-sphenoidal surgery and even more frequently observed post-radiation therapy of the pituitary gland. Patients with acromegaly might therefore present with deficiency of one or more pituitary hormones. As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones, other than GH/IGF-1, cannot be ruled out. Therefore, monitoring of pituitary

function (e.g. TSH/free T₄, ACTH) prior to initiation of therapy with Signifor LAR and periodically during treatment should be conducted as clinically appropriate.

Hypocortisolism

Treatment with Signifor LAR can lead to suppression of ACTH (adrenocorticotrophic hormone) secretion. Infrequent cases of hypocortisolism have been reported in clinical studies with pasireotide in acromegaly patients. It is therefore recommended to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatremia or hypoglycemia). In case of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of treatment with Signifor LAR may be necessary.

Drug-drug interactions

Pasireotide may decrease the relative bioavailability of cyclosporine (see section INTERACTIONS). Concomitant administration of Signifor LAR and cyclosporine may require adjustment of the cyclosporine dose to maintain therapeutic levels of the drug.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Safety assessment was based on 491 acromegaly patients who received pasireotide (419 patients received Signifor LAR and 72 received Signifor s.c.) in Phase I, II and III studies. The safety profile of Signifor LAR is consistent with the somatostatin analogue class, except for the higher degree and frequency of glucose metabolism disorders seen with Signifor LAR.

Study C2305

In Study C2305, 358 patients who had not been previously treated medically and who had failed surgery, or for whom surgery was not an option (referred to as “medically naïve patients”) were randomized to receive Signifor LAR (starting dose of 40 mg with possibility to up-titrate to 60 mg) or Sandostatin LAR (starting dose of 20 mg with possibility to up-titrate to 30 mg) in a double-blinded fashion. Baseline demographic characteristics were well balanced between the treatment arms. The mean age was 45.4 years, with equal proportions of men and women. 60.3% were Caucasian. The mean duration of exposure to Signifor LAR across core and extension phase was 75 weeks (N=178).

The most frequent ADRs reported in the Signifor LAR and Sandostatin LAR arms core and extension phase were diarrhea (33.1% and 40.6%), cholelithiasis (30.9% and 36.7%), hyperglycemia (28.1% and 7.2%) and diabetes mellitus (19.7% and 3.9%). Common Toxicity Criteria (CTC) grade 3 or 4 ADRs reported for more than 2% of the patients in the Signifor LAR and Sandostatin LAR arms were diabetes mellitus (4.5% and 0%), diarrhea (0.6% and 2.8%) and hyperglycemia (2.2% and 0.6%).

ADRs reported in patients who crossed over to the other treatment arm in the Phase III study were similar to those reported in the core and extension.

Study C2402

In Study C2402, 198 patients who did not achieve biochemical control (GH \leq 2.5 microgram/L and normalized IGF-1) on therapy with first-generation SSAs (referred to as “inadequately controlled patients”) were randomized to receive Signifor LAR 40 mg, Signifor LAR 60 mg

(both double-blind), or to the active control arm (continue with their prior treatment: Sandostatin LAR or lanreotide ATG open label). The demographic characteristics were balanced between the three treatment arms. The mean age is around 45 years, with approximately equal proportion of men and women. The majority of patients in all arms were Caucasian. The mean duration of exposure in the core phase of Study C2402 was 24 weeks for all treatment groups.

The most frequent ADRs observed in Signifor LAR 40 mg, 60 mg and active control in the 24-week core phase of study C2402 were hyperglycemia (33.3%, 29.0% and 6.1%), diabetes mellitus (19.0%, 25.8% and 4.5%) and diarrhea (11.1%, 19.4 and 1.5%). CTC grade 3 or 4 ADRs reported for more than 2% of the patients in Signifor LAR 40 mg, 60 mg and active control were hyperglycemia (11.1%, 8.1% and 0%), diabetes mellitus (0%, 3.2% and 0%) and abdominal pain (1.6%, 0%, 0%).

Tabulated summary of adverse drug reactions from clinical trials

Table 1 presents adverse reactions reported for patients being treated for at least 26 months in the core and extension phase of the Phase III study C2305 and for 24 weeks in the core phase of the Phase III study C2402, suspected to be drug related by the investigators and with a frequency higher than 5% in any of the Signifor treatment arms of the 2 studies and other notable ADRs which occurred in the two Phase III studies with a frequency of equal or less than 5%. Patient discontinued earlier were included.

ADRs are listed according to MedDRA primary System Organ Class. Within each System Organ Class, ADRs are ranked by frequency, with the most frequent reactions first. Frequencies were defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 1 Adverse drug reactions for Phase III study C2305 core and extension phase in medically naïve and Phase III study C2402 in inadequately controlled acromegaly patients with frequency of at least 5% in any Signifor LAR treatment arm of either study and other notable ADRs which occurred in the two Phase III studies with a frequency of equal or less than 5%.

Adverse drug reactions	C2305 core and extension (mean duration of exposure 75 weeks) Medically naïve patients	C2402 core (mean duration of exposure 24 weeks) Inadequately controlled patients		Frequency category
	Signifor LAR 40 mg ¹ n (%) N=178	Signifor LAR 40 mg n (%) N=63	Signifor LAR 60 mg n (%) N=62	
Blood and lymphatic disorders				
Anemia	4 (2.2)	2 (3.2)	0 (0.0)	Common
Endocrine disorders				
Adrenal insufficiency ²	2 (1.1)	1 (1.6)	0 (0.0)	Common
Metabolism and nutrition disorders				
Hyperglycemia	50 (28.1)	21 (33.3)	18 (29.0)	Very common

Diabetes mellitus	35 (19.7)	12 (19.0)	16 (25.8)	Very common
Type 2 diabetes mellitus	11 (6.2)	0 (0.0)	2 (3.2)	Common
Glucose tolerance impaired	3 (1.7)	1 (1.6)	3 (4.8)	Common
Decreased appetite	6 (3.4)	0 (0.0)	0 (0.0)	Common
Nervous system disorders				
Dizziness	12 (6.7)	4 (6.3)	1 (1.6)	Common
Headache	9 (5.1)	1 (1.6)	1 (1.6)	Common
Cardiac disorders				
Sinus bradycardia ³	16 (9.0)	0 (0.0)	0 (0.0)	Common
QT prolongation	4 (2.2)	0 (0.0)	0 (0.0)	Common
Gastrointestinal disorders				
Diarrhea	59 (33.1)	7 (11.1)	12 (19.4)	Very common
Abdominal pain	23 (12.9)	4 (6.3)	3 (4.8)	Very common
Abdominal distension	17 (9.6)	1 (1.6)	0 (0.0)	Common
Nausea	15 (8.4)	1 (1.6)	2 (3.2)	Common
Vomiting	7 (3.9)	1 (1.6)	0 (0.0)	Common
Hepatobiliary disorders⁴				
Cholelithiasis	55 (30.9)	6 (9.5)	7 (11.3)	Very common
Cholecystitis ⁵	5 (2.8)	0 (0.0)	0 (0.0)	Common
Skin and subcutaneous tissue disorders				
Alopecia	28 (15.7)	1 (1.6)	4 (6.5)	Very common
General disorders and administration site conditions				
Injection site reaction	14 (7.9)	0 (0.0)	1 (1.6)	Common
Fatigue	8 (4.5)	1 (1.6)	2 (3.2)	Common
Investigations				
Blood creatine phosphokinase increased	17 (9.6)	0 (0.0)	1 (1.6)	Common
Blood glucose increased	15 (8.4)	3 (4.8)	4 (6.5)	Common
Transaminases increased ⁶	11 (6.2)	0 (0.0)	1 (1.6)	Common
Alanine aminotransferase increased	10 (5.6)	0 (0.0)	1 (1.6)	Common
Aspartate aminotransferase increased	7 (3.9)	0 (0.0)	0 (0.0)	Common
Gamma glutamyltransferase increased	0	0 (0.0)	1 (1.6)	Common
Glycosylated hemoglobin increased	10 (5.6)	0 (0.0)	2 (3.2)	Common

Lipase increased	8 (4.5)	0 (0.0)	0 (0.0)	Common
Blood amylase increased	2 (1.1)	0 (0.0)	0 (0.0)	Common

¹Dose increase to 60 mg of Signifor LAR was permitted after the first three or six months of treatment (steady-state reached) if biochemical parameters showed a mean GH level ≥ 2.5 microgram/L and/or IGF-1 >ULN (age and sex related)

² Adrenal insufficiency also includes hypocortisolism

³Sinus bradycardia also includes Bradycardia

⁴Cholestasis was reported in Cushing's disease, though not reported in these Acromegaly clinical studies

⁵Cholecystitis also includes Cholecystitis acute

⁶Transaminases increased includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma glutamyltransferase increased and Transaminases increased. Prothrombin time prolonged was reported in Cushing's disease clinical studies, and there were no events suspected to be drug related by investigators reported in Acromegaly clinical studies

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reaction has been derived from post-marketing experience with Signifor LAR. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known.

Table 2 Adverse drug reaction derived from post-marketing experience (frequency not known)

Metabolism and nutrition disorders
Diabetic ketoacidosis

Description of selected adverse drug reactions

Glucose metabolism disorders

Elevated fasting glucose level was the most frequently reported CTC grade 3/4 laboratory abnormality in the Phase III study C2305.

In the core and extension phase of this study, CTC Grade 3 elevated fasting glucose levels were reported in 9.6% and 0.6% and CTC Grade 4 in 0.6% and 0 patients treated with Signifor LAR and Sandostatin LAR, respectively. In C2305, the mean absolute increase in FPG and HbA1c was similar for all patients treated with Signifor LAR irrespective of baseline values.

Mean FPG and HbA1c levels peaked within the first 3 months of treatment with Signifor LAR. In the core and extension phase of study C2305, adverse reactions of diabetes mellitus and hyperglycemia led to study discontinuation in 3 patients (1.7%) versus 2 (1.1%) and in 2 (1.1%) vs. 0 patients in the Signifor LAR and Sandostatin LAR arm, respectively. The elevations of fasting plasma glucose and HbA1c observed with Signifor LAR treatment are reversible after discontinuation, as shown by the rapid decrease in FPG and HbA1c levels in patients who crossed from Signifor LAR to Sandostatin LAR in the extension of study C2305. FPG and HbA1c stabilized at levels comparable to those seen in patients treated with Sandostatin LAR in the core phase of the study.

In study C2402, CTC grade 3 elevated fasting glucose levels were reported in 14.3% and 17.7% of patients in the Signifor LAR 40 mg and 60 mg group respectively, and none in the active control group. Hyperglycemia related adverse reactions led to study discontinuation in 6

patients (4.8%) in the Signifor LAR arm only (2 patients (1.6%) in 40 mg and 4 patients (3.2%) in 60 mg).

Monitoring of blood glucose levels in patients treated with Signifor LAR is recommended (see section WARNINGS AND PRECAUTIONS).

Gastrointestinal disorders

Gastrointestinal disorders were frequently reported with the use of Signifor LAR. These events were usually of low grade, required no intervention and improved with continued treatment. Gastrointestinal disorders were less frequent in inadequately controlled patients as compared to medically naïve patients.

Injection site reactions

In the Phase III studies, injection site reaction-related AEs (e.g. injection site pain, injection site discomfort) were all grade 1 or 2 in severity and were comparable between Signifor LAR and Sandostatin LAR treated patients. The incidence of such events was highest in the first 3 months of treatment. Injection site reaction-related AEs were less frequent in inadequately controlled patients as compared to medically naïve patients.

QT prolongation

In Study C2305 the proportion of patients with newly occurring notable QT/QTc intervals was comparable between Signifor LAR and Sandostatin LAR groups up to crossover, with few notable outlying values. No patient had a QTcF value >500 ms. QTcF >480 ms was reported for 3 vs. 2 patients in the Signifor LAR and Sandostatin LAR groups, respectively, and QTcF >60 ms prolonged from baseline was reported for 2 vs. 1 patient in the respective groups. In Study C2402, the only notable outlier was a QTcF value >480 ms in one patient in the Signifor LAR 40 mg group.

Liver enzymes

Transient elevations in liver enzymes have been reported with the use of somatostatin analogs 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 s.c. formulation, however not in patients with acromegaly treated with Signifor LAR. All observed cases of concurrent elevations were identified within ten days of initiation of treatment. The individuals recovered without clinical sequelae and liver function test results returned to baseline values after discontinuation of treatment.

Monitoring of liver enzymes is recommended prior and during treatment with Signifor LAR (see section WARNINGS AND PRECAUTIONS), as clinically appropriate.

Pancreatic enzymes

Asymptomatic elevations in lipase and amylase have been 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 analogs due to the association between cholelithiasis and acute pancreatitis.

INTERACTIONS

Pasireotide has moderate protein binding and is metabolically highly stable. Pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein), but is not an inducer of P-gp. In addition, at therapeutic dose levels, pasireotide is not expected to be:

- a substrate, inhibitor or inducer of CYP450 (cytochrome P450);
- a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1) and OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1;
- an inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1), influx transporter OAT1 or OAT3, OATP 1B1 or 1B3, and OCT1 or OCT2, efflux transporter P-gp, BCRP, MRP2 (multi-drug resistance protein 2) or BSEP (bile salt export pump).

Based on these *in vitro* data, the potential for protein binding, metabolism and/or transporter mediated DDI is low between pasireotide and co-medications *in vivo*.

The influence of a P-gp inhibitor on pharmacokinetics of pasireotide administered as Signifor s.c. injection has been tested in a drug-drug interaction study with co-administration of verapamil in healthy volunteers. No change in the rate or extent of pasireotide availability was observed.

Caution is required when co-administering Signifor LAR with anti-arrhythmic medicines and other drugs that may prolong the QT interval (See section WARNING AND PRECAUTIONS).

Anticipated interactions resulting in effects on other drugs

Limited published data suggest that somatostatin analogs might have an indirect effect in decreasing the metabolic clearance of compounds metabolized by CYP450 enzymes, via suppression of growth hormone secretion. The possibility that pasireotide may exert such an indirect effect cannot be excluded based on available data. Caution should be exercised when administering pasireotide concomitantly with drugs possessing a low therapeutic index and which are metabolized mainly by CYP3A4 (e.g. quinidine, terfenadine).

In dogs, pasireotide has been found to decrease blood level of cyclosporine by reducing its intestinal absorption. It is unknown whether such interaction occurs in humans. Therefore dose adjustments of cyclosporine may be required when co-administering pasireotide and cyclosporine (see section WARNINGS AND PRECAUTIONS).

Limited data with other somatostatin analogues suggest that co-administration with bromocriptine may increase the availability of bromocriptine. Available data cannot exclude the possibility that pasireotide may exert such an effect.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential and contraceptive measures

Animal studies have shown pasireotide to be harmful to the developing fetus. Women of child bearing potential are recommended to use effective contraception during treatment with pasireotide, and should also be advised that treatment with pasireotide may lead to improved fertility (see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY, sub section 'fertility').

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in animals with pasireotide via the s.c. route have shown reproductive toxicity (see section NON-CLINICAL SAFETY DATA). The potential risk for humans is not known. Signifor LAR should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Labor and delivery

No data in humans are available. Studies in rats with pasireotide via the s.c. route have shown no effects on labor and delivery (see section NON-CLINICAL SAFETY DATA).

Breast-feeding

It is not known whether pasireotide is excreted in human milk. Available data in rats with pasireotide via the s.c. route have shown excretion of pasireotide in milk (see section NON-CLINICAL SAFETY DATA). As a risk to the breast-fed child cannot be excluded, Signifor LAR should not be used by the nursing mother.

Fertility

Studies in rats with pasireotide via the s.c. route have shown effects on female reproductive parameters (see section NON-CLINICAL SAFETY DATA). The clinical relevance of these effects in humans is unknown.

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients treated with pasireotide may lead to improved fertility.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Somatostatin and analogues, H01CB05

Mechanism of action

Pasireotide is a novel cyclohexapeptide, injectable somatostatin analogue. Like 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 (SSTR). Five human somatostatin receptor subtypes are known: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogues bind to SSTR receptors with different potencies (Table 3). Pasireotide binds with high affinity to four of the five SSTRs.

Table 3 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and lanreotide to the five human SSTR receptor subtypes (SSTR1-5)

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
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	> 100	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

Results are the mean±SEM of IC50 values expressed as nmol/L (nM).

Pharmacodynamics (PD)

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumors where hormones are excessively secreted including growth hormone in acromegaly. Due to its broad binding profile to somatostatin receptors, pasireotide has the potential to stimulate both SSTR2 and SSTR5 subtype receptors relevant for inhibition of GH and IGF-1 secretion and therefore to be more effective for the treatment of acromegalic patients compared to other somatostatin analogues.

Glucose metabolism

In a randomized double-blinded mechanism study conducted in healthy volunteers, the development of hyperglycemia with pasireotide administered as Signifor s.c. at doses of 600 and 900 microgram twice a day was related to significant decreases in insulin secretion as well as incretin hormones (i.e. Glucagon-like peptide-1 [GLP-1] and glucose-dependent insulintropic polypeptide [GIP]). Pasireotide did not affect insulin sensitivity. In another randomized study conducted in healthy volunteers, the effects of pasireotide on blood glucose were investigated by comparison between administration of Signifor s.c. 600 microgram twice a day alone and with co-administration of an anti-hyperglycemic drug (metformin, nateglinide, vildagliptin or liraglutide, respectively. Insulin was not studied) over a 7-day period. Incretin-based therapy (GLP-1 agonists and DDP-IV inhibitors) was most efficacious in treating pasireotide-associated hyperglycemia in healthy volunteers.

Cardiac Electrophysiology

The effect of pasireotide (administered as Signifor s.c.) on the QT interval was assessed in two controlled, crossover thorough QT studies. In the first study that investigated a dose of 1,950 microgram administered twice a day, the maximum mean placebo-subtracted QTcF change

from baseline ($\Delta\Delta QTcF$) was 17.5 ms (90%CI: 15.53; 19.38). In the second study that investigated doses of 600 microgram and 1,950 microgram twice a day, the maximum mean placebo-subtracted $QTcI$ changes from baseline ($\Delta\Delta QTcI$) were 13.19 ms (90%CI: 11.38; 15.01) and 16.12 ms (90%CI: 14.30; 17.95), respectively. In both studies the maximum placebo-subtracted mean change from baseline occurred at 2 hours post dose. Both Signifor doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for the dose of 600 microgram twice a day (-10.39 bpm), and at 0.5 hours for 1,950 microgram twice a day (-14.91 bpm). No episodes of torsade de pointes were observed.

The predicted peak concentrations for the maximum Signifor LAR dose of 60 mg in acromegaly patients with normal liver function and of 40 mg in acromegaly patients with moderate hepatic impairment of 25.8 ng/mL and 28.8 ng/mL, respectively, are similar to the observed peak concentration (24.3 mg/mL) of Signifor s.c. 600 microgram twice a day and below the observed peak concentration (80.6 ng/mL) of the 1,950 microgram twice a day dose.

The increase in QT interval with administration of pasireotide is not mediated by an effect on the hERG potassium channel. Cardiac restitution, the ability of the heart to recover from each preceding beat, was measured on the continuous 24-hour ECGs to determine the effect of pasireotide on arrhythmia vulnerability. Pasireotide significantly improved all restitution parameters in the presence of QT prolongation indicating that pasireotide mediated QT prolongation may not be associated with an increased pro-arrhythmic risk. Further, quantitative T wave morphological analysis showed no changes indicative of impaired spatial heterogeneity of cardiac repolarization during pasireotide treatment.

Pharmacokinetics (PK)

Absorption

The relative bioavailability of pasireotide administered as Signifor LAR over pasireotide administered as Signifor s.c. is complete. Based on data of ~100% absolute bioavailability for pasireotide s.c. from pre-clinical studies in rats and monkeys, the absolute bioavailability of pasireotide administered as Signifor LAR is predicted to be complete in humans.

Food effect is unlikely to occur since Signifor LAR is administered via the parenteral route.

Distribution

In healthy volunteers, pasireotide administered as Signifor LAR is widely distributed with a large apparent volume of distribution ($V_z/F > 100$ L). Distribution between blood and plasma is concentration independent and shows that pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

Pasireotide has low passive permeability and is likely to be a substrate of P-gp, but the impact of P-gp on ADME (absorption, distribution, metabolism, excretion) of pasireotide is expected to be low. At therapeutic dose levels, pasireotide is not expected to be a substrate of BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), nor OATP (organic anion-transporting polypeptides) 1B1, 1B3, or 2B1.

Biotransformation/metabolism

Pasireotide was shown to be highly metabolically stable in human liver and kidney microsomes. In healthy volunteers, pasireotide in its unchanged form is the predominant form found in plasma, urine and feces.

Elimination

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route. In a human ADME study with pasireotide administered as Signifor s.c. with a single dose of 600 microgram $55.9 \pm 6.63\%$ of the radioactivity dose was recovered over the first 10 days post dosing, including $48.3 \pm 8.16\%$ of the radioactivity in feces and $7.63 \pm 2.03\%$ in urine.

The apparent clearance (CL/F) of pasireotide administered as Signifor LAR in healthy volunteers is on average 4.5 to 8.5 L/h.

Steady-state pharmacokinetics

PK steady state for pasireotide administered as Signifor LAR is achieved after three months. Following multiple i.m. doses every 4 weeks (q28d), Signifor LAR demonstrates approximately dose-proportional PK exposures in the dose range of 20 mg to 60 mg every 4 weeks in patients with acromegaly.

Special populations:**Geriatric patients (65 years of age or older)**

Age is not a significant covariate in the population PK analysis of patients with acromegaly.

Data on patients with acromegaly older than 65 years are limited but do not suggest any clinically significant differences in safety and efficacy in relation to younger patients.

Pediatric patients

No studies have been performed in pediatric patients.

Patients with renal impairment

Renal clearance has a minor contribution to the elimination of pasireotide in humans. Mild and moderate renal impairment is not expected to significantly impact the circulating levels of pasireotide, but it cannot be excluded that systemic exposure is increased in severe renal impairment.

Patients with hepatic impairment

In a clinical study with single dose administration of 600 µg pasireotide administered as Signifor s.c. in subjects with impaired hepatic function, subjects with moderate and severe hepatic impairment (Child-Pugh B and C) showed significantly higher exposures than subjects with normal hepatic function. AUC_{inf} was increased by 60% and 79%, C_{max} increased by 67% and 69%, and CL/F decreased by 37% and 44%, respectively, in the moderate and severe hepatic impairment groups relative to the control group.

Demographics

Population PK analyses of pasireotide administered as Signifor LAR suggest that race, gender and body weight do not have clinically relevant influence on PK parameters. No dose adjustment is required for demographics.

CLINICAL STUDIES

Medically naïve patients, Study C2305

A Phase III multicenter, randomized, blinded study was conducted to assess the safety and efficacy of Signifor LAR vs. Sandostatin LAR in medically naïve patients with active acromegaly. A total of 358 patients were randomized and treated. Patients were randomized in a 1:1 ratio to one of two treatment groups in each of the following two strata: 1) patients who have undergone one or more pituitary surgeries but have not been treated medically or 2) *de-novo* patients presenting a visible pituitary adenoma on MRI who refuse pituitary surgery or for whom pituitary surgery is contraindicated.

The two treatment groups were well balanced in terms of baseline demographics and disease characteristics. 59.7% and 56% of patients in Signifor LAR and Sandostatin LAR treatment groups respectively, were patients without previous pituitary surgery (*de-novo*). Average age of patients was approximately 45 years. Females constituted 52% of the patients in both treatment groups 59.7% of patients in the Signifor LAR group and 61.0% of patients in the Sandostatin LAR group were Caucasian.

The starting dose was 40 mg for Signifor LAR and 20 mg for Sandostatin LAR. 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 microgram/L and/or IGF-1 $> \text{ULN}$ (age and sex related). Maximum allowed dose was 60 mg for Signifor LAR and 30 mg for Sandostatin LAR.

Core phase

The primary efficacy endpoint was the proportion of patients with a reduction of mean GH level to < 2.5 microgram/L and the normalization 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 Signifor LAR and Sandostatin LAR, respectively demonstrating a statistically significant superior result favoring Signifor LAR (p-value = 0.007) (Table 4).

Table 4 Key results at Month 12 (Study C2305)

	Signifor LAR n (%) N=176	Sandostatin LAR n (%) N=182	p-value
GH < 2.5 microgram/L and normalized IGF-1*	31.3%	19.2%	p=0.007
GH < 2.5 microgram/L and IGF-1 $\leq \text{ULN}$	35.8%	20.9%	-
Normalized IGF-1	38.6%	23.6%	p=0.002
GH < 2.5 microgram/L	48.3%	51.6%	p=0.536

* Primary endpoint (patients with IGF-1 $<$ lower limit of normal (LLN) were not considered as "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 Signifor LAR arm than in the Sandostatin LAR arm (30.1% and 21.4%) and was maintained in all subsequent evaluations during the core phase.

Among patients with at least one dose increase, 12.4% of the patients in the Signifor LAR treatment arm and 8.9% in the Sandostatin LAR treatment arm achieved biochemical control.

At month 12, reduction in tumor volume was comparable between treatment groups and in patients with and without previous pituitary surgery. Ninety-eight percent of patients treated with SIGNIFOR LAR had either a reduction or no change in tumor volume from baseline assessed by MRI at month 12. The median (range) change in tumor volume was a reduction of 39.8% (-97.6% to 16.9%). The proportion of patients with a reduction of tumor volume greater than 20% at Month 12 was 80.8% for Signifor LAR and 77.4% for Sandostatin LAR.

Health related quality of life measured by AcroQoL was evaluated at baseline and at month 12. At month 12, there were statistically significant improvements in the Physical, Psychological-Appearance and the Global AcroQoL scores in both Signifor LAR and Sandostatin LAR treatment groups. The mean improvements from baseline were greater for Signifor LAR than for Sandostatin LAR but the difference in changes from baseline to month 12 between the treatment groups were not statistically significant. Additionally, ring size and five acromegaly symptoms (i.e. headache, fatigue, perspiration, paresthesia and osteoarthritis) were scored from 0 (no symptom) to 4 (very severe) each month at both time points. At month 12, there were reductions in ring size and all five symptom severity scores in both treatment groups compared to baseline, with no statistically significant differences between the two treatment groups.

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 medication they were initially randomized to.

During the extension phase, 74 patients continued receiving Signifor LAR and 46 patients continued with Sandostatin LAR treatment. At month 25, 48.6% of patients (36/74) in the Signifor LAR group and 45.7% (21/46) in the Sandostatin LAR group achieved biochemical control. At the same time point, 70.3% and 80.4% of patients in the Signifor LAR arm and in the Sandostatin LAR arm respectively had mean GH values <2.5 microgram/L; and normalization of IGF-1 was achieved by 51.4% and 47.8% of patients, respectively. The percentage of patients achieving biochemical control, including those patients with IGF-1 < LLN was 60.8% (45/74) in the Signifor LAR group and 52.2% (24/46) in the Sandostatin LAR group.

During the extension phase, tumor volume continued to decrease and improvements in acromegaly signs and symptoms remained comparable between the two treatments arms. AcroQoL scores remained numerically higher in the Signifor LAR than the Sandostatin LAR arm throughout the extension phase.

Inadequately Controlled Patients

Study C2402

Study C2402 was a Phase III, multicenter, randomized, parallel-group, three-arm study of double-blind Signifor LAR 40 mg and Signifor LAR 60 mg versus open-label Sandostatin LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly. A total of 198 patients were randomized to receive Signifor LAR 40 mg (n=65), Signifor LAR 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 C2402 are defined as patients with a mean GH concentration of a 5-point profile over a 2-hour period >2.5 microgram/L and sex- and age-adjusted IGF-1 $>1.3 \times$ upper limit of normal (ULN). Patients had to be treated with maximum indicated doses of Sandostatin LAR (30 mg) or lanreotide ATG (120 mg) for at least 6 months prior to randomization. Baseline demographic and disease characteristics were balanced between the treatment arms, with a mean age around 45 years, approximately equal proportion of men and women, and median time since diagnosis of approximately 4 years. Three-quarters of patients had previously been treated with Sandostatin LAR and a quarter with lanreotide ATG. 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 microgram/L, 12.1 microgram/L and 9.5 microgram/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 microgram/L and normalization of sex- and age-adjusted IGF-1) at week 24 with Signifor LAR 40 mg or 60 mg versus continued treatment with active control (Sandostatin LAR 30 mg or lanreotide ATG 120 mg), separately. The study met its primary efficacy endpoint for both Signifor LAR doses. The proportion of patients achieving biochemical control, was 15.4% (p-value = 0.0006) and 20.0% (p-value <0.0001) for Signifor LAR 40 mg and 60 mg, respectively at 24 weeks compared with zero in the active control arm (Table 5).

Table 5 Key results at Week 24 (Study C2402)

	Signifor LAR 40 mg N=65 n (%), p value	Signifor LAR 60 mg N=65 n (%), p value	Active Control N=68 n (%)
GH <2.5 microgram/L and normalized IGF-1*	10 (15.4%), p=0.0006	13 (20.0%), p <0.0001	0 (0%)
Normalization of IGF-1	16 (24.6%), p <0.0001	17 (26.2%), p <0.0001	0 (0%)
GH <2.5 microgram/L	23 (35.4%)	28 (43.1%)	9 (13.2%)

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

In patients treated with Signifor LAR where reductions in GH and IGF-1 levels were observed, these changes occurred rapidly and were maintained up to Week 24, which is consistent with what was observed in medically naïve patients in Study C2305.

The proportion of patients with a reduction or no change in pituitary tumor volume at Week 24 was 81.0% and 70.3% on Signifor LAR 40 and 60 mg, and 50.0% on active control. The median (range) change in tumor volume was a reduction of -10.4% (-74.5% to 19.4%) and -6.3% (-66.7% to 14.5%) from baseline for SIGNIFOR LAR 40 mg and 60 mg, respectively. Furthermore, a higher proportion of patients on Signifor LAR (18.5% and 10.8% for 40 mg and 60 mg, respectively) than active comparator (1.5%) achieved a reduction in tumor volume of at least 25%.

Health related quality of life measured by AcroQoL was evaluated at baseline and at week 24. At week 24, there was an improvement in the Physical, Psychological-Appearance and the Global AcroQoL scores in both Signifor LAR 40 mg and 60 mg treatment groups. In the Signifor LAR 40 group, these changes were statistically significant for the AcroQoL Physical sub-score. In the Signifor LAR 60 mg these changes were statistically significant for the Physical, Psychological-Appearance and Global scores. There were no statistically significant differences for the Sandostatin LAR or Lanreotide ATG group. The mean improvement from baseline was greatest in the Signifor LAR 60 mg group for all scores. However, the difference in changes from baseline to week 24 between the treatment groups was not statistically significant.

C2305 Crossover phase

At the end of the core phase, patients not adequately responding to their initial therapy were allowed to switch to the other treatment.

81 patients were crossed over from Sandostatin LAR to Signifor LAR, and 38 patients were crossed over from Signifor LAR to Sandostatin LAR. 12 months after crossover, the percentage of patients achieving biochemical control was 17.3% (14/81) for Signifor LAR and 0% (0/38) for Sandostatin LAR. The percentage of patients achieving biochemical control, including those patients with IGF-1 < LLN was 25.9% in the Signifor LAR group and 0% in the Sandostatin LAR group.

12 months after crossover, the response rates for reduction of GH (GH < 2.5 microgram/L) were 44.4% and 23.7% in patients treated with Signifor LAR and Sandostatin LAR respectively; response rates for IGF-1 were 27.2 and 5.3% respectively. Mean GH levels decreased markedly for patients who crossed to Signifor LAR while mean GH increased over time for patients who crossed to Sandostatin LAR. Mean IGF-1 levels decreased over time in patients who crossed to Signifor LAR, while the mean IGF-1 level in patients crossed to Sandostatin LAR remained elevated.

Further decrease in tumor volume was observed 12 months after crossover for both treatment groups, and it was higher in patients who crossed over to Signifor LAR (-24.7%) than in patients who crossed over to Sandostatin LAR (-17.9%).

Improvements from crossover baseline in severity scores of acromegaly symptoms were noted for both crossover treatments.

NON-CLINICAL SAFETY DATA

Non-clinical safety studies conducted with pasireotide via the s.c. route included safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction and development. Additionally, tolerability and repeated dose toxicity studies were conducted with pasireotide LAR via the i.m. route. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. Effects in non-clinical studies were observed at exposures considered similar to or in excess of the maximum human exposure.

In safety pharmacology studies (with pasireotide via the s.c. route), pasireotide had no adverse effects on respiratory or cardiovascular functions. Decreases in general and behavioral activity were observed in mice at the dose of 12 mg/kg, equivalent to approximately 32-fold of the maximum recommended therapeutic human dose (MHRD) for pasireotide s.c., or 27-fold of the estimated maximum daily dose for pasireotide LAR, based on surface area.

Pasireotide was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella* and *E. coli*. and mutation test in human peripheral lymphocytes). Pasireotide was not genotoxic in an *in vivo* rat bone marrow nucleus test at doses up to 50 mg/kg, approximately 250-fold the maximum recommended therapeutic human dose (MHRD) for pasireotide s.c., or 224-fold of the estimated maximum daily dose for pasireotide LAR, based on surface area, mg/m².

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

In embryo-fetal development studies in rats and rabbits with pasireotide via the s.c. route, pasireotide was not teratogenic at maternally toxic doses (respectively 10 and 5 mg/kg/day) leading to exposures (AUC_{0 to 24 hrs}) respectively 144- and 40-fold higher than the MHRD for pasireotide s.c., or 106- and 29.6-fold higher than MHRD for pasireotide LAR. At 10 mg/kg/day in rats, the frequency of early/total resorptions and malrotated limbs was increased. At 5 mg/kg/day in rabbits, increased abortions, reduced fetal weights and ensuing skeletal variations were observed. Reduced fetal weight and ensuing delayed ossification were seen at 1 mg/kg/day (4.8-fold higher exposure than MHRD for pasireotide LAR). Pasireotide had no effects on labor and delivery in rats administered up to 10 mg/kg/day (45-fold higher than the MHRD for pasireotide LAR based on surface area, mg/m²). Available toxicological data in animals have shown excretion of pasireotide in milk. Retardation of physiological growth, attributed to GH inhibition was observed at 2 mg/kg/day (10-fold higher than the MHRD for pasireotide s.c., or 9-fold higher than estimated maximum daily dose for Signifor-LAR, based on surface area, mg/m²) during a pre- and postnatal study in rats. After weaning, body weight gains in the rat pups exposed to pasireotide were comparable to controls, showing reversibility. Pasireotide did not affect fertility in male rats at doses up to 10 mg/kg/day (a dose 52-fold higher than the MHRD for pasireotide s.c., or 45-fold higher than the estimated maximum daily dose for Signifor-LAR, based on surface area, mg/m²). In female rats, as expected from the pharmacology of pasireotide, fertility was decreased at daily doses of 0.1 mg/kg/day (0.6-fold the maximum recommended therapeutic human dose for pasireotide s.c., or 0.5-fold of the estimated maximum daily dose of pasireotide LAR, based on surface area, mg/m²) as shown by decreased numbers of corpora lutea and implantation sites. Abnormal cycles or acyclicity were observed at 1 mg/kg/day (5-fold higher than the MHRD for pasireotide s.c., or 4.5-fold higher than the estimated maximum daily dose for pasireotide LAR, based on surface area, mg/m²).

INCOMPATIBILITIES

Signifor LAR powder for suspension for injection is to be used as a single dose container, without any dilution with other products. Therefore, no compatibility data with other products have been generated.

STORAGE

See folding box.

Store at 2 to 8°C.

Do not freeze.

Signifor LAR should not be used after the date marked "EXP" on the pack.

Signifor LAR must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE

Instructions for preparation and intramuscular injection of Signifor LAR

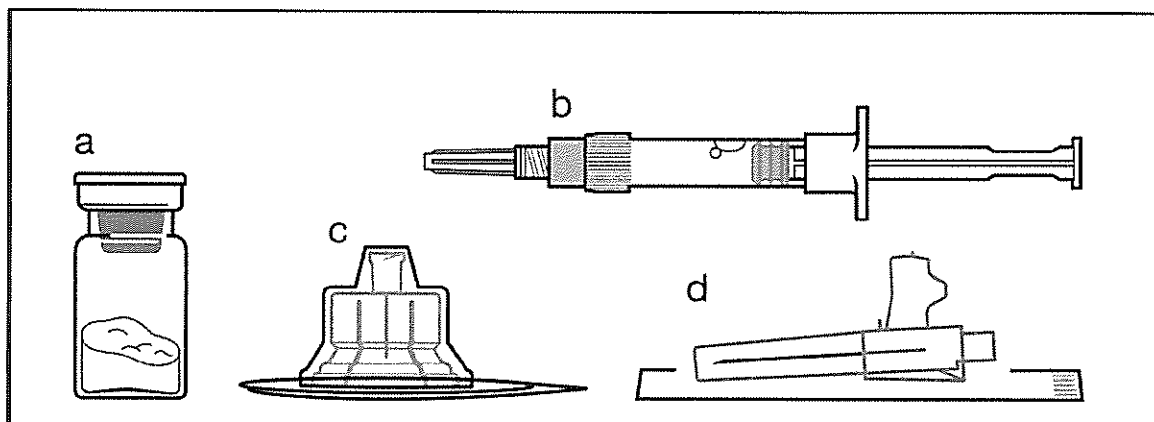
FOR DEEP INTRAMUSCULAR INJECTION ONLY

ATTENTION:

There are 2 critical steps in the reconstitution of Signifor LAR. **Not following them could result in failure to deliver the drug 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 diluent solution, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until uniform suspension is formed.**

Included in the injection kit:



a One vial containing Signifor LAR powder

b One prefilled syringe containing the diluent solution for reconstitution

c One vial adapter for drug product reconstitution

d One safety injection needle (20G x 1.5")

Follow the instructions below carefully to ensure proper reconstitution of Signifor LAR before deep intramuscular injection.

Signifor LAR suspension must only be prepared **immediately** before administration.

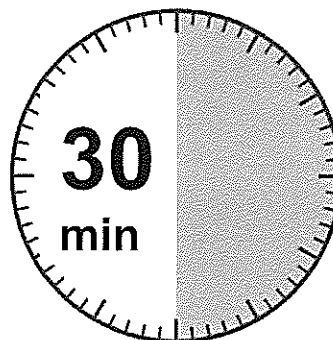
Signifor LAR should only be administered by a trained health professional.

Step 1

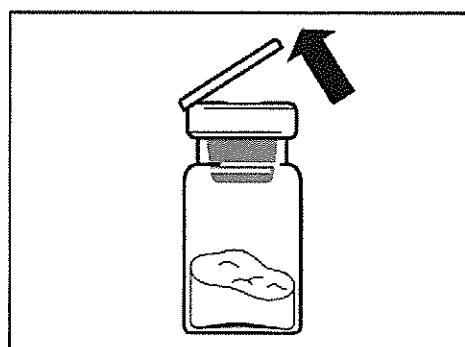
Remove the Signifor LAR injection kit from refrigerated storage.

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: The injection kit can be re-refrigerated if needed.

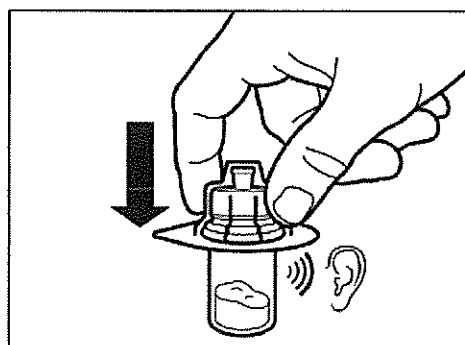
**Step 2**

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

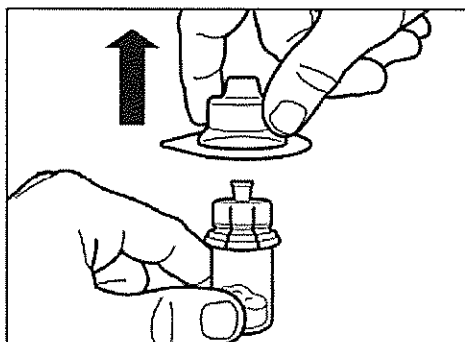


Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.

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 an audible “click”.

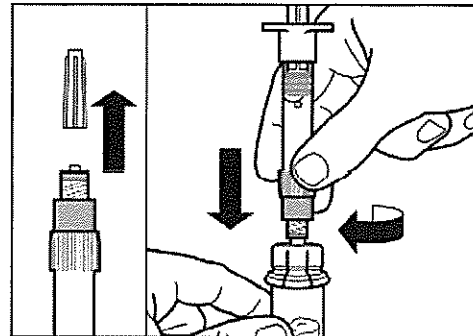


Lift the packaging off the vial adapter with a vertical movement.

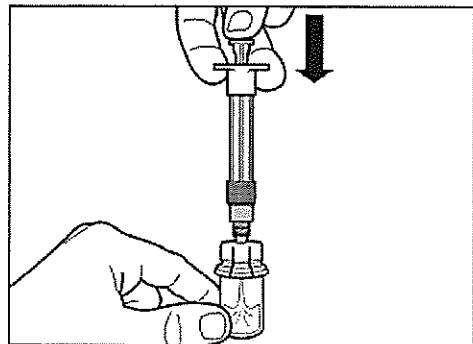


Step 3

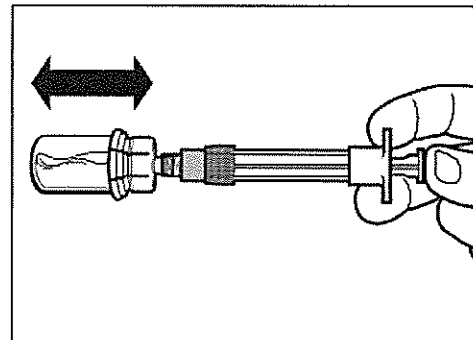
Remove the cap from the syringe prefilled with diluent solution and **screw** the syringe onto the vial adapter.



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

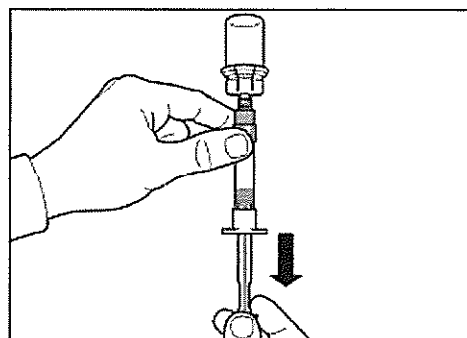
**Step 4**

ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction 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.

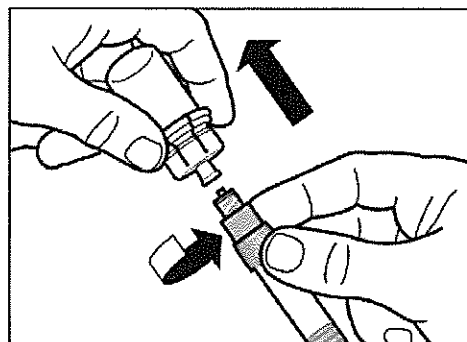


Step 5

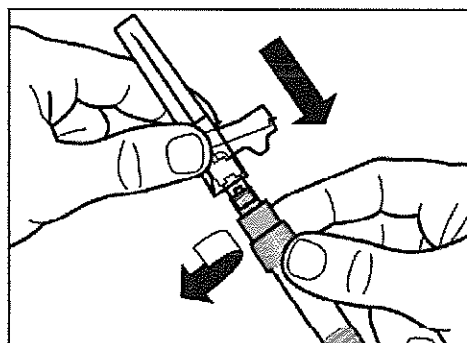
Turn syringe and vial upside down, **slowly** pull the plunger back and draw the entire content from the vial into the syringe.



Unscrew the syringe from the vial adapter.

**Step 6**

Screw the safety injection needle onto the syringe.

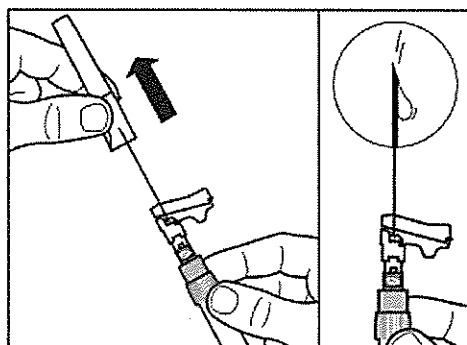


Pull the protective cover straight off the needle.

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 LAR is now ready for **immediate** administration.



Step 7

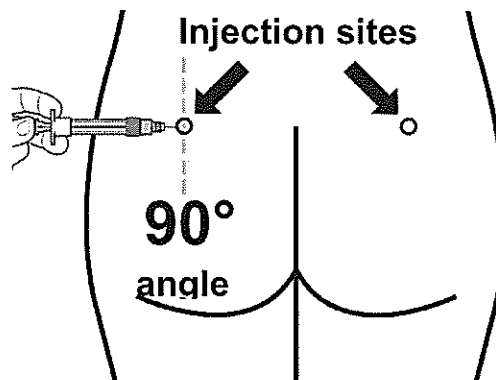
Signifor LAR must be given only by deep intramuscular injection; **NEVER** intravenously.

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).

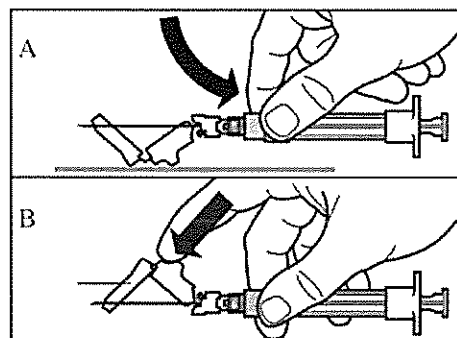
**Step 8**

Activate the safety guard over the needle, in one of the 2 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.

**Manufacturer:**

See folding box.

International Package Leaflet

Information issued: January 2020.SIN

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