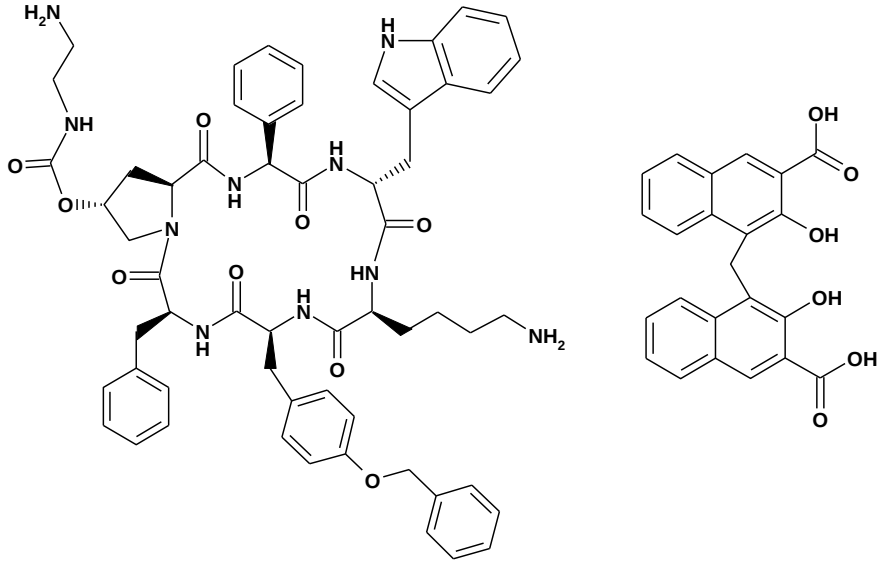
SIGNIFOR LAR®

Pasireotide embonate

NAME OF MEDICINE

SIGNIFOR LAR® 20 mg, 40 mg or 60 mg modified release injection plus diluent.

Pasireotide embonate



Pasireotide embonate CAS No.: 396091-79-5

Pasireotide CAS No.: 396091-73-9

Molecular weight: 1047.21 + 388.37 = 1435.58 (for the embonate salt)

Pasireotide embonate is a white to yellowish powder. The drug substance is practically insoluble in water. pKa values for pasireotide base are pKa 1 = 10.2 and pKa 2 = 9.1 (water/dioxane in 0.15 M KCl at 25 °C).

DESCRIPTION

Signifor LAR is a modified release injection dosage form (also known as Long Acting Release) for intramuscular (i.m.) administration. It is a slightly yellowish to yellowish powder consisting of pasireotide distributed within polymer microparticles to be suspended in vehicle

prior to injection. Each vial contains: 20, 40, or 60 mg pasireotide (as embonate), polyglactin and polyglactin glucose.

The vehicle used to suspend the powder is a 2 mL clear, colourless to slightly yellow or slightly brown diluent in a prefilled syringe. The diluent excipients are mannitol, carmellose sodium, poloxamer and water for injections.

The appearance of the constituted suspension is milky, slightly yellowish to yellowish and homogeneous suspension, pH is 5.0 - 8.0.

PHARMACOLOGY

Mechanism of Action

Pasireotide is a 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 1). Pasireotide binds with high affinity to four of the five SSTRs.

Table 1 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide and lanreotide to the five human SSTR receptor subtypes (SSTR1-5)

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	> 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 IC_{50} values expressed as nmol/L (nM).

Pharmacodynamics

Somatostatin receptors are expressed in many tissues, especially in neuroendocrine tumours 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.

Glucose metabolism

In a randomised double-blinded mechanism study conducted in healthy volunteers, the development of hyperglycaemia 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 insulinotropic polypeptide [GIP]). Pasireotide did not affect insulin sensitivity.

In another randomised study conducted in healthy volunteers, the effects of pasireotide on blood glucose were investigated by comparison between administrations of Signifor s.c. 600 microgram twice a day alone and with co-administration of an anti-hyperglycaemic drug (metformin, vildagliptin or liralgutide, 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 hyperglycaemia in healthy volunteers.

Cardiac electrophysiology:

The effect of pasireotide (administered as Signifor s.c.) on the QT interval was assessed in two cross-over dedicated QT studies. In the first study that investigated a dose of 1950 microgram b.i.d. dose, the maximum mean placebo-subtracted QTcF change from baseline (ΔΔQTcF) was 17.5 ms (90% CI: 15.53; 19.38). In the second study, that investigated doses of 600 microgram b.i.d. and 1950 microgram b.i.d., the maximum mean placebo-subtracted QTcI changes from baseline (ΔΔQTcI) were 13.19 ms (90% CI: 11.38; 15.01) and 16.12 ms (90% CI: 14.30; 17.95 ms), 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 b.i.d. (-10.39 bpm) and at 0.5 hours for 1950 microgram b.i.d. (-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 ng/mL) of Signifor s.c. 600 microgram b.i.d. and below the observed peak concentration (80.6 ng/mL) of the 1950 microgram b.i.d.

Further, quantitative T wave morphological analysis showed no changes indicative of impaired spatial heterogeneity of cardiac repolarisation during pasireotide treatment. The mechanism for the observed QT prolongation is not known. Pasireotide has not been demonstrated to inhibit hERG potassium channels, and detailed analyses of continuous 24-hour ECG recordings suggest that pasireotide does not impair cardiac restitution.

Pharmacokinetics

Absorption:

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

Relative bioavailability of pasireotide administered as Signifor LAR over pasireotide administered s.c. as Signifor is complete.

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

Distribution:

In healthy volunteers, pasireotide administered as Signifor LAR is widely distributed with 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.

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 faeces.

Excretion:

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 ± 6.63% of the radioactivity dose was recovered over the first 10 days post dosing, including 48.3 ± 8.16% of the radioactivity in faeces and 7.63 ± 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:

Elderly patients in the target population:

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 (a total of 19 out of 306 acromegaly patients treated with Signifor LAR were at least 65 years old in the two Phase III studies) but do not suggest any clinically significant differences in safety and efficacy in relation to younger patients.

Paediatric patients:

No studies have been performed in paediatric patients.

Patients with renal impairment:

Clinical studies have not been performed in patients with renal impairment. However, renal clearance has a minor contribution to the elimination of pasireotide in humans. Renal function (creatine clearance and estimated glomerular filtration rate) is not a covariate in the population PK analysis. Therefore renal function is not expected to significantly impact the circulating levels of pasireotide.

Patients with hepatic impairment:

In a clinical study, a single 600 microgram dose of pasireotide was 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. Upon correction for covariate effect (age, BMI and albumin) 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 (Caucasian, Black, Asian, Native American, and others), gender and body weight do not have clinically relevant influence on PK parameters. No dose adjustment is required for demographics.

CLINICAL TRIALS

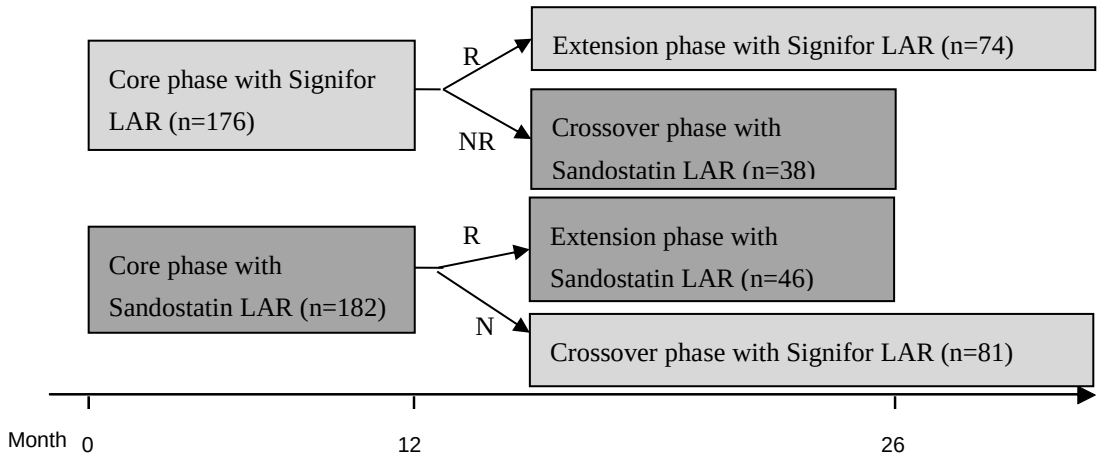
Medically naïve patients, Study C2305

A Phase III multicentre, randomised, 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 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 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 >ULN (age and sex related). Maximum allowed dose was 60 mg for Signifor LAR and 30 mg for Sandostatin LAR (Figure 1).

Figure 1 Study design – Study C2305



R: Responder / NR: Non-Responder. The decision of continuing in the same treatment arm or switching to the other arm was based on both responder status and at the discretion of the investigator.

Core phase

The primary efficacy endpoint in this superiority study was the proportion of patients with a reduction of mean GH level to <2.5 microgram/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 Signifor LAR and Sandostatin LAR, respectively demonstrating a statistically significant superior result favouring Signifor LAR (p-value = 0.007), with normalisation of IGF-1 being the main driver for the superiority of Signifor LAR over Sandostatin LAR in terms of biochemical response (Table 2).

Table 2 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 normalised IGF-1*	**31.3%**	**19.2%**	**p=0.007**
GH<2.5 microgram/L and IGF-1 ≤ULN	**35.8%**	**20.9%**	**-**
Normalised 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 tumour volume was comparable between 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 Signifor LAR and 77.4% for Sandostatin LAR.

Health related quality of life, a secondary endpoint, measured by AcroQol was evaluated at baseline and at month 12. At month 12, the changes in AcroQoL scores from baseline was numerically higher in Signifor LAR than Sandostatin LAR for the global score as well as the 4 sub-scores (physical, psychological, psychological/appearance, and psychological/ personal relations sub-scores), with the largest difference between the treatment arms seen for the psychological sub-score and the largest change from baseline seen for the psychological/appearance sub-score. The difference between Signifor LAR and Sandostatin LAR was not statistically significant for the global score or for any of the sub-scores.

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 randomised to (Figure 1).

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 normalisation 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, tumour 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, multicentre, randomised, 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 randomised 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 × 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 randomisation. 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 in this superiority study was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 microgram/L and normalisation 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 3).

Table 3 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 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 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 tumour volume at Week 24 was 81.0% and 70.3% on Signifor LAR 40 and 60 mg, and 50.0% on active control. 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 tumour volume of at least 25%.

Health related quality of life, a secondary endpoint 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; specifically, the Signifor 40 mg group displayed significant improvements in the Physical sub-score, while the Signifor 60 mg group displayed significant improvements in the Physical, Psychological-Appearance and Global scores. 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.

Inadequately Controlled Patients, 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 (Figure 1).

Eighty one (81) patients were crossed over from Sandostatin LAR to Signifor LAR, and 38 patients were crossed over from Signifor LAR to Sandostatin LAR. Twelve (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.

Twelve (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 tumour 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%).

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 or who are inadequately controlled on treatment with other somatostatin analogues.

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh C).

PRECAUTIONS

Effects on Fertility

Reduction in growth hormone (GH) levels and normalisation of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients treated with pasireotide may affect fertility. Women of childbearing potential should be informed of this possibility and are recommended to use effective contraception during treatment with pasireotide.

Studies in rats with pasireotide via the s.c. route have shown effects on female reproductive parameters. The clinical relevance of these effects in humans is unknown.

In female rats, fertility was decreased at daily doses of 0.1 mg/kg/day by s.c. injection as shown by decreased numbers of implantation sites and viable foetuses. This dose equates to 0.42- fold the estimated maximum daily dose of pasireotide LAR based on surface area, mg/m^2. Decreased corpora lutea and abnormal cycles or acyclicity were observed at 1 mg/kg/day by s.c. injection. This dose equates to 4.2-fold higher than the estimated maximum daily dose for pasireotide LAR based on surface area, mg/m^2. This effect is consistent with the pharmacological action of pasireotide to inhibit IGF-1 secretion.

Pasireotide did not affect fertility in male rats at subcutaneous doses up to 10 mg/kg/day. This dose equates to 42-fold higher than the estimated maximum daily dose for Signifor LAR based on surface area, mg/m^2.

Use in Pregnancy – Category B3

There are no adequate and well-controlled studies in pregnant women and women of child bearing age. Studies in animals have shown evidence of an increased occurrence of fetal damage. The potential risk for humans is not known. Women of child-bearing potential are recommended to use effective contraception during treatment with pasireotide.

In embryofetal development studies in rats and rabbits, no direct teratogenic effect of pasireotide was observed at maternally toxic doses (respectively 10 and 5 mg/kg/day by subcutaneous injection) leading to exposures (plasma AUC) respectively 106 and 30-fold higher than the plasma AUC at the MRHD for pasireotide LAR. At 10 mg/kg/day in rats, the frequency of early/total resorptions and mal-rotated limbs was increased, fetal weight was decreased and ossification was impaired. 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 also seen in rabbits at 1 mg/kg/day by s.c. injection (4.8-fold higher the plasma AUC at the MRHD for pasireotide LAR).

Labour and delivery:

No data in humans are available.

Pasireotide had no effects on labour and delivery in rats administered up to 10 mg/kg/day sub-cutaneously (42-fold higher than the MRHD for pasireotide LAR based on surface area, mg/m^2).

Signifor should be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus.

Use in Lactation:

It is not known whether pasireotide is excreted in human milk. Available data in rats have shown excretion of pasireotide in milk. As a risk to the breastfed child cannot be excluded, Signifor LAR should not be used by the nursing mother.

Retardation of physiological growth, attributed to GH inhibition was observed at all doses tested (≥2 mg/kg/day by subcutaneous injection) in a pre- and postnatal study in rats. This dose equates to ≥8-fold the maximum daily dose for Signifor LAR based on surface area, mg/m^2. After weaning, body weight gains in the rat pups exposed to pasireotide were comparable to controls, showing reversibility.

Paediatric Use

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

Use in the Elderly

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 Pharmacology)

Hypocortisolism

Treatment with Signifor LAR can lead to suppression of ACTH (adrenocorticotropic hormone) secretion. Suppression of ACTH may lead to a decrease in circulating levels of

cortisol and potentially hypocortisolism. Infrequent cases of hypocortisolism-related AEs (2.3%; 7 out of 303 patients in two Phase III studies), particularly in patients with abnormal cortisol levels prior to initiation of pasireotide, have been reported in clinical studies with Signifor LAR 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 hypoglycaemia). 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.

Hyperglycaemia/hypoglycaemia and Diabetes

Elevations in blood glucose levels have been seen in healthy volunteers and patients treated with pasireotide. In medically naïve patients treated with Signifor LAR the frequency of hyperglycaemia-related adverse events was 57.3% and in inadequately controlled patients 66.7% (40 mg) and 61.3% (60 mg). In acromegaly patients who developed hyperglycaemia, the condition generally appeared to respond to antidiabetic therapy. Dose reductions or discontinuation of treatment with pasireotide due to hyperglycaemia were infrequent in clinical studies with pasireotide (see Section Adverse Effects, Description of Selected Adverse Drug Reactions).

Hypoglycaemia was also observed in subjects participating in clinical trials with pasireotide (see Adverse effects) but less frequently than hyperglycaemia (5.1%, 3.2% and 6.5% in medically naïve and inadequately controlled patients (40 mg and 60 mg doses), respectively).

Glycaemic status (fasting plasma glucose/haemoglobin A1c [FPG/HbA1c]) should be assessed prior to starting treatment with pasireotide. FPG/HbA1c monitoring during treatment should follow established guidelines. Self-monitoring of blood glucose and/or FPG assessments should be done weekly for the first three months and periodically thereafter, as clinically appropriate as well as over the first four to six weeks after any dose increase. After treatment discontinuation, glycaemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

If hyperglycaemia 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 hyperglycaemia. The optimal treatment for the management of Signifor-induced hyperglycaemia is not known. If uncontrolled hyperglycaemia persists despite appropriate medical management the dose of Signifor LAR should be reduced or the treatment discontinued.

Patients with poor glycaemic control (as defined by HbA1c values >8% while receiving anti-diabetic therapy) may be at a higher risk of developing severe hyperglycaemia and associated complications, e.g. ketoacidosis. Because of this predictable adverse reaction, diabetes

management and monitoring should be intensified prior to initiation and during Signifor LAR therapy.

In patients with uncontrolled diabetes mellitus intensive anti-diabetic therapy should be initiated prior to treatment with Signifor LAR. During treatment, additional monitoring and dose adjustments of the anti-diabetic therapy (including insulin) may be necessary.

Cardiovascular Related Events

Bradycardia has been reported with the use of pasireotide (see Adverse effects). 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, including quantitative ECG beat to beat restitution analysis, showed that pasireotide does not alter cardiac repolarisation in the same manner as drugs known to prolong QT that are associated with pro-arrhythmia (see 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 hypokalaemia 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. Hypokalaemia or hypomagnesemia must be corrected prior to Signifor administration and should be monitored periodically during therapy.

Liver Tests

Mild transient elevations in aminotransferases are commonly observed in healthy subjects and 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 Adverse effects).

Monitoring of liver function is recommended prior to treatment with Signifor LAR and after the first 2 to 3 weeks and then monthly for 3 months. 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 is a recognised adverse drug reaction associated with long-term use of somatostatin analogues and has been frequently reported in clinical studies with pasireotide (see Adverse effects). 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 T_4, ACTH) prior to initiation of therapy with Signifor LAR and periodically during treatment should be conducted as clinically appropriate.

Genotoxicity

Pasireotide was not genotoxic in a battery of *in vitro* assays (Ames mutation test in bacteria and a test for clastogenicity in human peripheral lymphocytes). Pasireotide was not genotoxic in an *in vivo* rat bone marrow nucleus test at subcutaneous doses up to 50 mg/kg. This dose equates to 210-fold the maximum daily dose for pasireotide LAR based on body surface area (mg/m^2).

Carcinogenicity

Carcinogenicity studies by the subcutaneous route were (2 years duration) conducted in rats and transgenic mice (6 months). No carcinogenic activity was observed with pasireotide in transgenic mice, involving administration of doses up to 2.5 mg/kg/day (yielding plasma AUC values 8-10 times higher than in patients at the maximum recommended human dose [MRHD]. Injection site tumours (fibromas) were increased in incidence in male rats at a dose of 0.3 mg/kg/day. This finding is consistent with a response to continuous irritation/inflammation at the repeatedly injected site and is not considered to indicate a carcinogenic potential in humans. No treatment-related increase in systemic tumours in male rats or tumours in female rats was seen up to the highest dose tested (0.3 mg/kg/day; yielding 10 times [males] and 5 times [females] the plasma AUC in patients at the MRHD.

INTERACTIONS WITH OTHER MEDICINES

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 all 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.

Anticipated Interactions Resulting in Effects on Other Drugs

Limited published data suggest that somatostatin analogues might have an indirect effect in decreasing the metabolic clearance of compounds metabolised 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 metabolised mainly by CYP3A4 (e.g. quinidine, terfenadine).

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

Anticipated pharmacokinetic interactions resulting in effects on pasireotide

In vitro, pasireotide has been shown to be a P-gp substrate. There is potential for strong P-gp inhibitors, e.g. ketoconazole, cyclosporin, verapamil, clarithromycin, to increase concentrations of pasireotide but the clinical implications of this potential effect are not known.

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, disopyramide), class III antiarrhythmics (e.g. amiodarone, dronedarone, sotalol), certain antibacterials (intravenous erythromycin, pentamidine injection, clarithromycin, moxifloxacin), certain antipsychotics (e.g. chlorpromazine, fluphenazine, haloperidol, amisulpride, sertindole, methadone), certain antihistamines (e.g. terfenadine), antimalarials (e.g. chloroquine, lumefantrine), certain antifungals (ketoconazole, except in shampoo) (see also section Precautions).

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, propranolol, sotalol), anticholinergics (e.g. ipratropium bromide, oxybutynin), certain calcium channel blockers (e.g. verapamil, diltiazem), certain antiarrhythmics (see also section Precautions).

Insulin and anti-diabetic medicinal products

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

Growth hormone receptor antagonists

No data are available for the concomitant medication with growth hormone receptor antagonists.

ADVERSE EFFECTS

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 hyperglycaemia 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 randomised 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 diarrhoea (33.1% and 40.6%), cholelithiasis (30.9% and 36.7%), hyperglycaemia (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%), diarrhoea (0.6% and 2.8%) and hyperglycaemia (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 ≤2.5 microgram/L and normalised IGF-1) on therapy with first-generation SSAs (referred to as "inadequately controlled patients") were randomised 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 hyperglycaemia (33.3%, 29.0% and 6.1%), diabetes mellitus (19.0%, 25.8% and 4.5%) and diarrhoea (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 hyperglycaemia (11.1%, 8.1% and 0%), diabetes mellitus (0%, 3.2% and 0%) and abdominal pain (1.6%, 0%, 0%).

Tables 4 and 5 present adverse events 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 with a frequency of at least 5%.

Table 4 Adverse Events [n (%)] With Frequency of at Least 5% in SIGNIFOR LAR in the Core and Extension Phase of the Phase III C2305 Study in Medical Naïve Acromegaly

	SIGNIFOR LAR n (%) N=178	**Sandostatin LAR n (%) N=180**
Diarrhoea	71 (40)	81 (45)
Cholelithiasis	58 (33)	71 (40)
Hyperglycaemia	55 (31)	18 (10)
Headache	41 (23)	49 (27)
Diabetes mellitus	39 (22)	8 (4)
Alopecia	34 (19)	36 (20)
Abdominal pain	33 (19)	44 (24)

Nasopharyngitis	32 (18)	29 (16)
Nausea	27 (15)	41 (23)
Blood creatine phosphokinase increased	25 (14)	24 (13)
Arthralgia	22 (12)	25 (14)
Back pain	22 (12)	22 (12)
Abdominal distension	21 (12)	22 (12)
Dizziness	21 (12)	20 (11)
Fatigue	20 (11)	21 (12)
Sinus bradycardia*	19 (11)	13 (7)
Vomiting	19 (11)	15 (8)
Hypertension	18 (10)	16 (9)
Blood glucose increased	17 (10)	6 (3)
Influenza	16 (9)	11 (6)
Upper respiratory tract infection	16 (9)	7 (4)
Alanine aminotransferase increased	15 (8)	10 (6)
Injection site reaction**	15 (8)	15 (8)
Anaemia	14 (8)	10 (6)
Pain in extremity	14 (8)	8 (4)
Abdominal pain upper	12 (7)	18 (10)
Aspartate aminotransferase increased	12 (7)	8 (4)
Type 2 diabetes mellitus	12 (7)	0 (0)
Flatulence	11 (6)	11 (6)
Glycosylated haemoglobin increased	11 (6)	5 (3)
Hypoglycaemia	11 (6)	14 (8)
Bronchitis	10 (6)	4 (2)
Constipation	10 (6)	19 (11)
Cough	10 (6)	17 (9)

Hepatic steatosis	10 (6)	11 (6)
Lipase increased	10 (6)	13 (7)
Urinary tract infection	10 (6)	13 (7)
Blood bilirubin increased	9 (5)	5 (3)
Electrocardiogram QT prolonged	9 (5)	10 (6)
Weight decreased	9 (5)	8 (4)
Muscle spasms	8 (5)	10 (6)
Oropharyngeal pain	8 (5)	15 (8)
Pyrexia	8 (5)	11 (6)
Gamma-glutamyltransferase increased	3 (2)	11 (6)

* Sinus bradycardia includes the following PTs: Bradycardia and sinus bradycardia.

** Injection site reaction includes the following PTs: Injection site pain, Injection site discomfort, Injection site reaction, Injection site erythema, Injection site hematoma, Injection site nodule, Injection site pruritus and Injection site swelling.

Other notable adverse reactions which occurred with a frequency of 5% or less for SIGNIFOR LAR were: decreased appetite (4%); adrenal insufficiency (3%); glucose tolerance impaired (1%); cholecystitis ((3%) includes cholecystitis acute); QT-prolongation (4%); blood amylase increased (2%).

Table 5 Adverse Events [n (%)] With Frequency of at Least 5% in any Treatment Arms in the Core a Phase of the Phase III C2402 Study in Inadequately Controlled Acromegaly Patients

	SIGNIFOR LAR 40 mg	SIGNIFOR LAR 60 mg	Active Control
	n (%)	n (%)	n (%)
Preferred term	N=63	N=62	N=66
Hyperglycaemia	21 (33)	19 (31)	9 (14)
Diabetes mellitus	13 (21)	16 (26)	5 (8)
Diarrhoea	10 (16)	12 (19)	3 (5)
Cholelithiasis	6 (10)	8 (13)	9 (14)
Nasopharyngitis	4 (6)	7 (11)	2 (3)
Abdominal pain	5 (8)	5 (8)	2 (3)
Alopecia	1 (2)	4 (7)	0
Blood glucose increased	3 (5)	4 (7)	0
Hypoglycaemia	2 (3)	4 (7)	0
Nausea	2 (3)	4 (7)	2 (3)
Glucose tolerance impaired	2 (3)	3 (5)	4 (6)
Anaemia	4 (6)	2 (3)	2 (3)
Headache	9 (14)	2 (3)	3 (5)
Dizziness	5 (8)	1 (2)	2 (3)
Atrioventricular block first degree	4 (6)	0	0

Other notable adverse reactions which occurred with a frequency of 5% or less in the SIGNIFOR LAR 40 mg, SIGNIFOR LAR 60 mg arm, respectively, were vomiting (3% and 0%), adrenal insufficiency (2% and 0%), transaminases increased (2% and 3%) and lipase increased (2% and 0%).

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 hyperglycaemia 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 stabilised 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. Hyperglycaemia 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 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 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 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 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 analogues due to the association between cholelithiasis and acute pancreatitis.

DOSAGE AND ADMINISTRATION

Dose

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.

Dose adjustment in:

Renal insufficiency:

No dosage adjustment is required in patients with impaired renal function (see Pharmacology).

Hepatic insufficiency:

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 Pharmacology). Signifor LAR should not be used in patients with severe hepatic impairment (Child Pugh C) (see Contraindications).

Paediatric patients:

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

Elderly patients:

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 Pharmacology).

Method of Administration

Signifor LAR should only be administered by deep intramuscular injection by a trained health care professional.

The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle (see Instructions for use and handling).

Signifor LAR suspension must only be prepared immediately before administration.

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.

Product is for single use in one patient only. Discard any residue.

Instructions for preparation and intramuscular injection of Signifor LAR

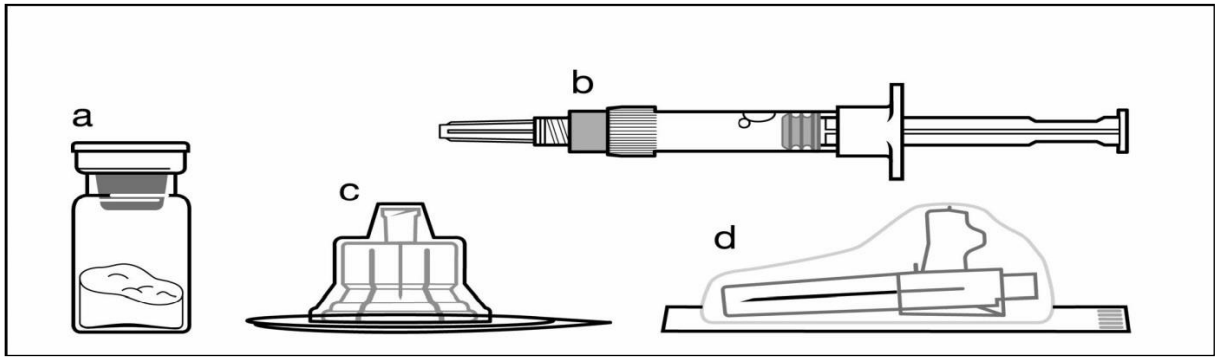
FOR DEEP INTRAMUSCULAR INJECTION ONLY

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

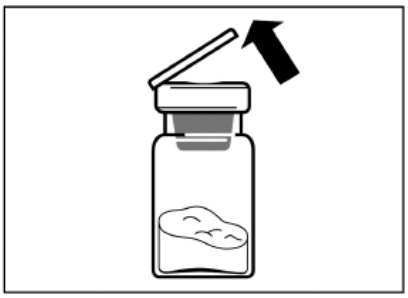
Remove the Signifor LAR injection kit from refrigerated storage.

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

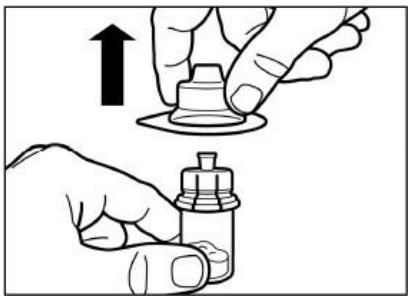
Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.



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

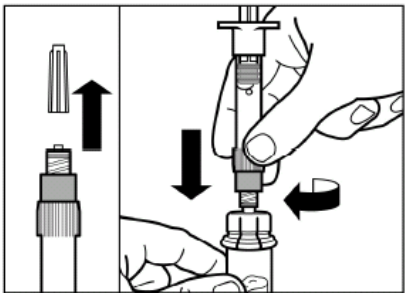
Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible “click”.

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

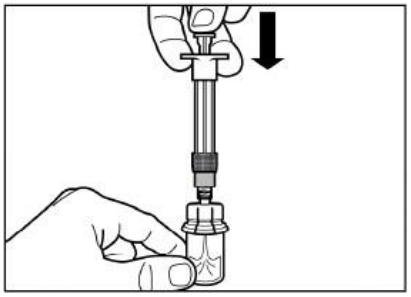


Step 3

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

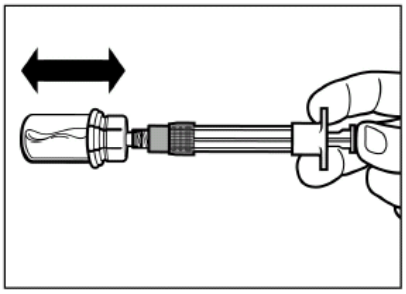


Slowly push the plunger all the way down to transfer all the diluent solution in the vial.



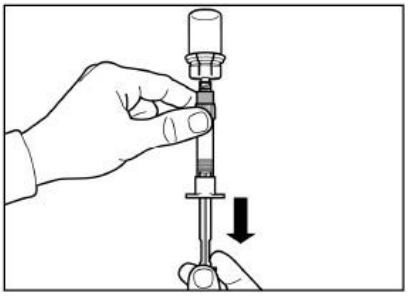
Step 4

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**.

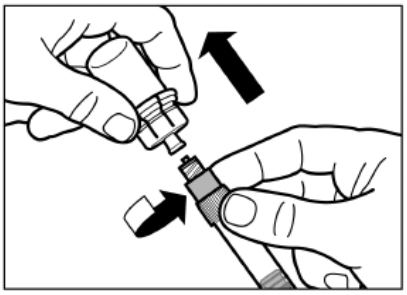


Step 5

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

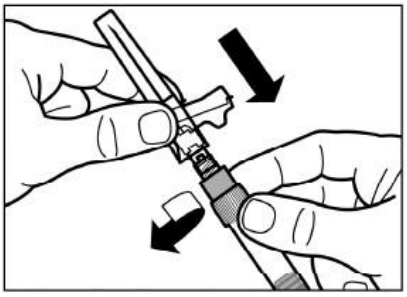


Unscrew the syringe from the vial adapter.



Step 6

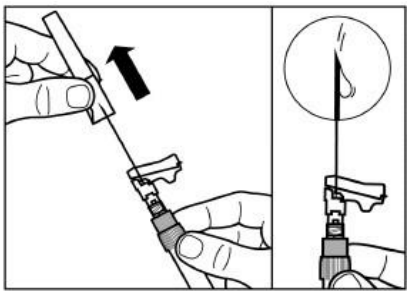
Screw the safety injection needle onto the syringe.



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

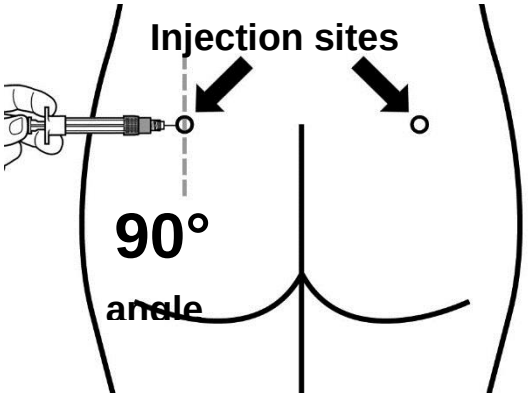
Signifor LAR must be given only by deep intramuscular injection; **NEVER** intravenously.

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).



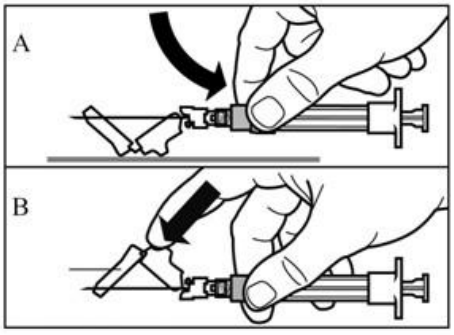
Step 8

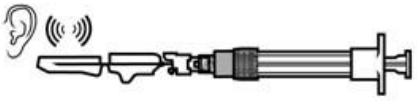
Activate the safety guard over the needle, in one of the 2 methods shown:

- 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.





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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (0800 POISON) in New Zealand for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Dosage form of the powder in the vial: injection, modified release

Dosage form of the vehicle used to suspend the powder in the vial: diluent

Quantity of active ingredient:

Each vial contains:

- 20 mg pasireotide (as embonate)
- 40 mg pasireotide (as embonate)
- 60 mg pasireotide (as embonate)

Container type:

Signifor LAR 20 mg, 40 mg and 60 mg powder is contained in a glass vial with rubber closure and flip-off cap.

The container of the diluent used to suspend the powder consists of a 3 mL colourless glass syringe which is closed with a grey front stopper and a grey plunger stopper (made of rubber).

Pack sizes:

Each dosage strength (20 mg, 40 mg or 60 mg pasireotide) of Signifor LAR modified release injection vial comes with one prefilled syringe containing 2 mL diluent, one vial adaptor and one safety injection.

Appearance:

Signifor LAR modified release powder for injection is a slightly yellowish to yellowish powder in a 6 mL brownish glass vial and grey flip-off cap. The flip-off cap colours indicate dosage strength (20 mg: grey, 40 mg: red, 60 mg: orange).

The vehicle is a clear, colourless to slightly yellow or slightly brown solution, filled into 3 mL colourless glass syringes.

The appearance of the reconstituted suspension is milky, slightly yellowish to yellowish and homogeneous suspension.

Storage Conditions

Store at 2-8 °C. Refrigerate do not freeze. Signifor LAR must be kept out of the reach and sight of children. Signifor LAR suspension must only be prepared immediately before administration.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd

54 Waterloo Road

Macquarie Park 2113

Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

04 May 2015

DATE OF MOST RECENT AMENDMENT

08 May 2017

Signifor® LAR is a registered trademark.

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