1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SIGNIFOR® LA 20 mg (powder for suspension for injection)

SIGNIFOR® LA 40 mg (powder for suspension for injection)

SIGNIFOR® LA 60 mg (powder for suspension for injection)

SIGNIFOR LA solvent for suspension for injection

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each vial contains:

SIGNIFOR LA 20 mg - 20 mg pasireotide (as pamoate)

SIGNIFOR LA 40 mg - 40 mg pasireotide (as pamoate)

SIGNIFOR LA 60 mg - 60 mg pasireotide (as pamoate)

Each pre-filled syringe contains:

SIGNIFOR LA solvent for suspension for injection

Excipients with known effect:

Contains sugar: Mannitol 90.0 mg in 2 ml solution.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

- **SIGNIFOR LA Powder:**

  Slight yellowish-to-yellowish powder in vial

- **SIGNIFOR LA Solvent for suspension for injection:**

  Clear, colourless to slightly yellow to slightly brown solution in pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acromegaly as second-line therapy after pituitary surgery (or when surgery is not feasible), in patients inadequately responding to other somatostatin analogues (SSAs) or where other SSAs cannot be used.

4.2 Posology and method of administration

Posology

General target population

- The recommended initial dose of SIGNIFOR LA is 40 mg administered by deep intramuscular injection every 4 weeks (28 days).
- 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 LA 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 LA.
- The dose may be decreased either temporarily or permanently by 20 mg decrements.

Missed dose

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

Special populations

Elderly patients (≥ 65 years):

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

Patients with renal impairment:

- No dose adjustment is required in patients with impaired renal function.

Patients with 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. SIGNIFOR LA should not be used in patients with severe hepatic impairment (Child Pugh C) (see section 4.3).

Paediatric patients

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

Method of administration

- SIGNIFOR LA should only be administered by deep intramuscular injection by a trained healthcare professional.
- SIGNIFOR LA 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 4.2 ‘Instructions for use’).

Instruction for use

Instructions for preparation and intramuscular injection of SIGNIFOR LA

FOR DEEP INTRAMUSCULAR INJECTION ONLY

ATTENTION:

There are 2 critical steps in the reconstitution of SIGNIFOR LA.

Not following them could result in failure to deliver the medicine appropriately.

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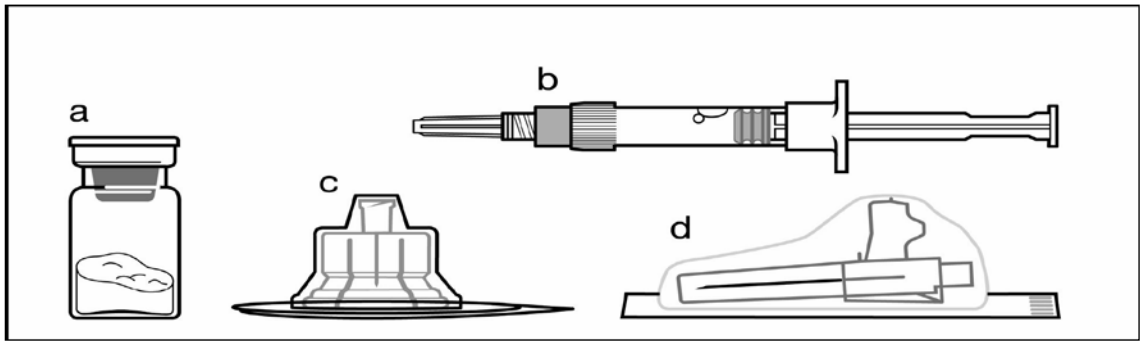
- **<u>The injection kit must reach room temperature</u>**. Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the diluent solution, **<u>shake the vial moderately</u>** in a horizontal direction for a minimum of 30 seconds **<u>until uniform suspension is formed</u>**.

Included in the injection kit:



a. One vial containing SIGNIFOR LA powder.

b. One pre-filled syringe containing the diluent solution for reconstitution.

c. One vial adapter for medicinal product reconstitution.

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

Follow the instructions below carefully to ensure proper reconstitution of SIGNIFOR LA before deep intramuscular injection:

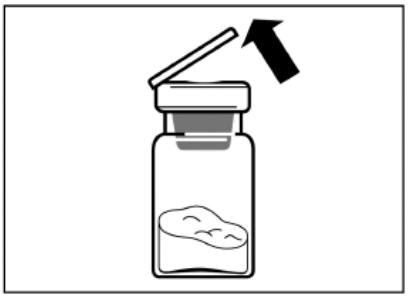
- SIGNIFOR LA suspension must only be prepared immediately before administration.
- SIGNIFOR LA should only be administered by a trained health professional.

Step 1

Remove the SIGNIFOR LA injection kit from refrigerated storage.

ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

Note: If not used within 24 hours, the injection kit can be returned to the fridge.



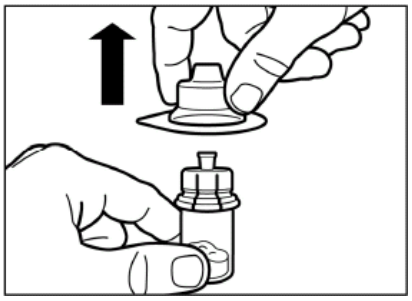
Step 2

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.

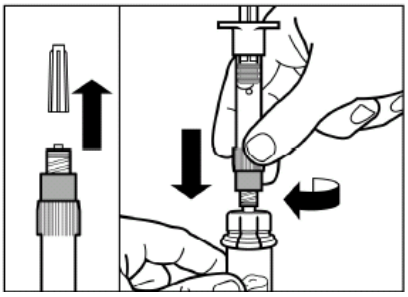
Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible “click”.

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

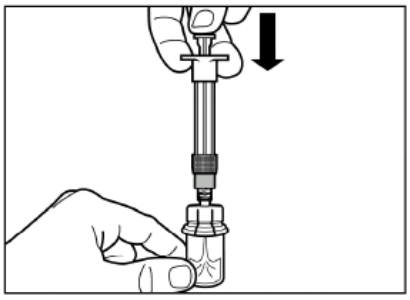


Step 3

Remove the cap from the syringe pre-filled with diluent solution and **screw** the syringe onto the vial adapter.

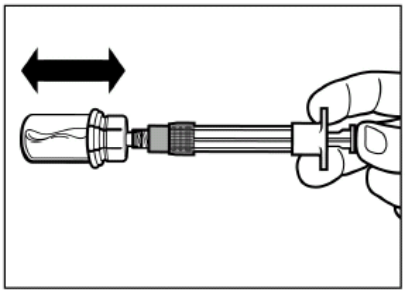


Slowly push the plunger all the way down to transfer all the diluent solution in the vial.



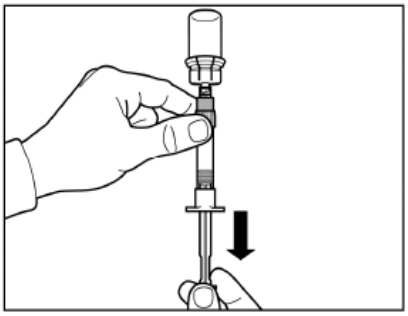
Step 4

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**.

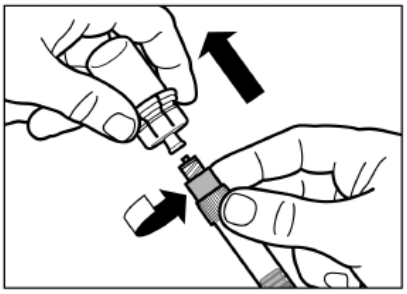


Step 5

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

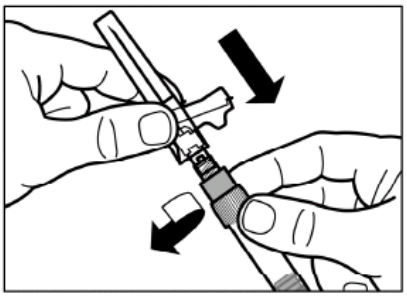


Unscrew the syringe from the vial adapter.



Step 6

Screw the safety injection needle onto the syringe.

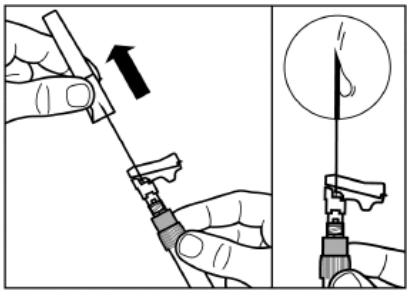


Pull the protective cover straight off the needle.

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



Step 7

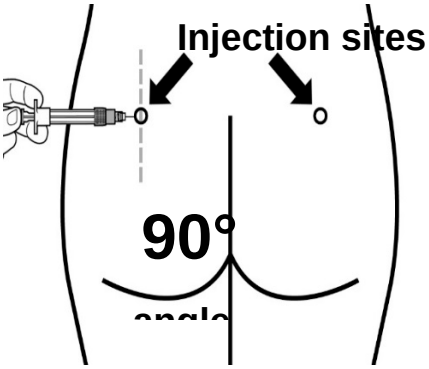
SIGNIFOR LA must be given only by deep intramuscular injection; **NEVER** intravenously.

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).

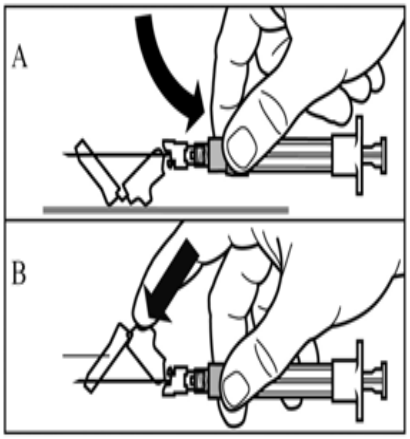
Slowly depress the plunger until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in Step 8).



Step 8

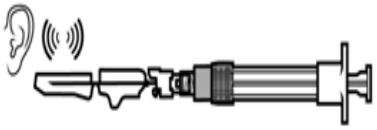
Activate the safety guard over the needle, in one of the 2 methods shown:

- 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.



4.3 Contraindications

- Hypersensitivity to pasireotide or any of the excipients of SIGNIFOR LA (see section 6.1).
- Severe hepatic impairment (Child Pugh C).

4.4 Special warnings and precautions for use

Glucose metabolism

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

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- In patients who developed hyperglycaemia, the condition generally appeared to respond to antidiabetic therapy. Dose reductions or discontinuation of treatment with pasireotide due to hyperglycaemia were infrequent in clinical studies with pasireotide.
- The development of hyperglycaemia appears to be related to decreases in secretion of insulin and of incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]).
- Glycaemic status (fasting plasma glucose/hemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with SIGNIFOR LA.
- FPG/HbA_{1c} monitoring during treatment should follow established guidelines.
- Self-monitoring of blood glucose and/or FPG assessments should be done weekly for the first three months and periodically thereafter, as clinically appropriate as well as over the first four to six weeks after any dose increase.
- Monitoring of FPG 4 weeks and HbA1c 3 months after the end of the treatment should be performed.
- If hyperglycaemia develops in a patient treated with SIGNIFOR LA, the initiation or adjustment of anti-diabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycaemia.
- If uncontrolled hyperglycaemia persists despite appropriate medical management the dose of SIGNIFOR LA should be reduced or the treatment discontinued (see section 4.5).
- There have been post-marketing cases of ketoacidosis with SIGNIFOR LA in patients with and without a history of diabetes. Patients who present with signs and symptoms

consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of diabetes history.

- Patients with poor glycaemic control (as defined by HbA1c values > 8 % while receiving anti-diabetic therapy), diabetes management and monitoring should be intensified prior to initiation and during SIGNIFOR LA therapy.

Liver tests

- Mild transient elevations in aminotransferases are commonly observed in patients treated with SIGNIFOR LA. Rare 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 4.8).
- Monitoring of liver function is recommended prior to treatment with SIGNIFOR LA, 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 LA 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.

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- Following discontinuation of treatment with SIGNIFOR LA, patients should be monitored until resolution. Treatment should not be restarted if the liver function abnormalities are suspected to be related to SIGNIFOR LA.

Cardiovascular related events

- Bradycardia has been reported with the use of pasireotide as contained in SIGNIFOR LA (see section 4.8).
- 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 medicines such as beta-blockers, calcium channel blockers, or medicines to control electrolyte balance, may be necessary (see section 4.5).
- Pasireotide has been shown to prolong the QT interval in healthy subjects.
- 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 medicines or other medicines that are known to lead to QT prolongation;
- hypokalaemia and/or hypomagnesaemia.

A baseline ECG is recommended prior to initiating therapy with SIGNIFOR LA.

Monitoring for an effect on the QTc interval is advisable 21 days after initiating therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to SIGNIFOR LA administration and should be monitored periodically during therapy.

Hypocortisolism

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

Gallbladder and related events

- Cholelithiasis (gallstones) is a recognised adverse medicine reaction associated with long-term use of somatostatin analogues and has frequently been reported in clinical studies with pasireotide (see section 4.8).
- There have been post-marketing cases of cholangitis in patients taking SIGNIFOR LA, 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 LA therapy is therefore recommended.
- The presence of gallstones in SIGNIFOR LA-treated patients is often largely asymptomatic. However, symptomatic stones should be managed according to clinical practice.

Pituitary hormones

- Deficiency of pituitary secreted hormones is common after trans-sphenoidal surgery and radiation therapy of the pituitary gland.
- As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones, other than GH and/or IGF-1 may occur.
- Therefore, monitoring of pituitary function (e.g. TSH/free T4) prior to initiation of therapy with SIGNIFOR LA and periodically during treatment should be conducted as clinically appropriate.

Effect on female fertility

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

Coagulation abnormalities

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

Renal impairment

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

Sodium content

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

4.5 Interaction with other medicines and other forms of Interaction

Anticipated pharmacokinetic interactions resulting in effects on pasireotide:

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

Anticipated pharmacokinetic interactions resulting in effects on other medicines:

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

Anticipated pharmacodynamic interactions:

Medicines that prolong QT interval

Caution is required when co-administering SIGNIFOR LA with medicines that may prolong the QT interval such as:

- class Ia dysrhythmics (e.g. quinidine, procainamide, disopyramide);

- class III dysrhythmics (e.g. amiodarone, dronedarone, sotalol, dofetilide, ibutilide),
- certain antibacterials (intravenous erythromycin, pentamidine injection, clarithromycin, moxifloxacin);
- certain antipsychotics (e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, tiapride, amisulpride, sertindole, methadone);
- certain antihistamines (e.g. terfenadine, astemizole, mizolastine);
- antimalarials (e.g. chloroquine, halofantrine, lumefantrine);
- certain antifungals (ketoconazole, except in shampoo) (see section 4.4).

Bradycardic medicines

Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving SIGNIFOR LA concomitantly with:

- bradycardic medicines, such as beta blockers (e.g. metoprolol, carteolol, propranolol, sotalol);
- acetylcholinesterase inhibitors (e.g. rivastigmine, physostigmine);
- certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil),
- certain antiarrhythmics (see also section 4.4).

Insulin and antidiabetic medicines

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

SIGNIFOR LA is not recommended for use in women of childbearing potential who are not using contraception (see section 4.4).

Pregnancy

Safety in pregnancy and lactation have not been established. Animal studies showed reproductive toxicity. There is a limited amount of data from the use of pasireotide in pregnant women.

Breastfeeding

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. As a risk to the breast-fed child cannot be excluded, SIGNIFOR LA should not be used by the nursing mother.

Fertility

It is unknown whether pasireotide has an effect on human fertility. Studies in rats with pasireotide via the s.c. route have shown effects on female reproductive parameters.

4.7 Effects on ability to drive and use machines

SIGNIFOR LA has minor influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

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Patients should be advised to be cautious when driving or using machinery if they experience fatigue, dizziness or headache during treatment with SIGNIFOR LA.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of pasireotide intramuscular use is consistent with the somatostatin analogue class, except for the higher degree and frequency of hyperglycaemia seen with pasireotide intramuscular use.

Acromegaly

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

Tabulated list of adverse reactions

The adverse reactions in Table 1 include events reported in the pivotal studies with the intramuscular formulation in patients with acromegaly and with Cushing's disease. Adverse reactions are listed according to MedDRA primary system organ class. Within each system

organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from the available data).

Table 1 Adverse reactions by preferred term for pasireotide intramuscular use

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders		Anaemia		
Endocrine disorders		Adrenal insufficiency*		
Metabolism and nutrition disorders	Hyperglycaemia, diabetes mellitus	Type 2 diabetes mellitus, glucose tolerance impaired, decreased appetite		Diabetic ketoacidosis
Nervous system disorders		Headache dizziness		

Cardiac disorders		Sinus bradycardia*, QT prolongation		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain*	Abdominal distension, vomiting		Steatorrhea Faeces discoloured
Hepatobiliary disorders	Cholelithiasis	Cholecystitis*, Cholestasis		
Skin and subcutaneous		Alopecia, pruritus		

tissue disorders				
General disorders and administration site conditions	Fatigue*	Injection site reaction*		
Investigations		increased glycosylated haemoglobin, increased alanine aminotransferase, increased blood glucose, increased blood creatine phosphokinase, increased lipase, increased aspartate aminotransferase, increased gamma-glutamyltransferase,	increased amylase, prolonged prothrombin time	

***Grouped terms:**

Adrenal insufficiency includes adrenal insufficiency and blood cortisol decreased.

Sinus bradycardia includes bradycardia and sinus bradycardia.

Abdominal pain includes abdominal pain and abdominal pain upper. Injection site reaction includes injection site pain, injection site nodule, injection site discomfort, injection site bruising, injection site pruritus, injection site reaction, injection site hypersensitivity and injection site swelling.

Cholecystitis includes cholecystitis acute and cholecystitis chronic.

Fatigue includes fatigue and asthenia.

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Description of selected adverse reactions

Glucose metabolism disorders

Acromegaly

In acromegaly patients elevated fasting glucose level was the most frequently reported grade 3/4 laboratory abnormality in the two-phase III studies. In study C2305, grade 3 elevated fasting glucose levels were reported in 9.7 % and 0.6 % and grade 4 in 0.6 % and 0 % of acromegaly patients treated with pasireotide intramuscular use and octreotide intramuscular use, respectively.

In study C2402, grade 3 elevated fasting glucose levels were reported in 14.3 % and 17.7 % of acromegaly patients treated with pasireotide intramuscular use 40 mg and 60 mg respectively, and in no patients in the active control group.

Two cases of hyperglycaemia-related emergencies (diabetic ketoacidosis and diabetic hyperglycaemic coma) were reported following a dose increase of pasireotide to 60 mg in medical treatment naïve patients; one in a patient with untreated hyperglycaemia and HbA1c > 8 % prior to initiation of pasireotide and the other in a patient with untreated hyperglycaemia and a fasting plasma glucose of 359 mg/dl, respectively. In both studies, mean FPG and HbA1c levels peaked within the first three months of treatment with pasireotide intramuscular use. In medically naïve patients (study C2305), the mean absolute increase in FPG and HbA1c was similar at most of the time points for all patients treated with pasireotide intramuscular use irrespective of baseline values.

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

control (octreotide intramuscular use or lanreotide deep subcutaneous injection). In a pooled analysis of the two pivotal studies, the overall incidence of hyperglycaemia-related adverse reactions was 58.6 % (all grades) and 9.9 % (CTC Grade 3 and 4) for SIGNIFOR LA intramuscular use versus 18.0 % (all grades) and 1.1 % (CTC Grade 3 and 4) for the active control. In the pivotal study with patients inadequately controlled on another somatostatin analogue, the proportion of patients not previously treated with anti-diabetic agents who required commencement of anti-diabetic therapy during the study was 17.5 % and 16.1 % in the SIGNIFOR LA 40 mg and 60 mg arms compared to 1.5 % in the active control arm. In the pivotal study with patients who did not receive prior medical treatment, the proportion of patients who required commencement of anti-diabetic therapy during the study was 36 % in the SIGNIFOR LA arm compared to 4.4 % in the active control arm.

Gastrointestinal disorders

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

Injection site reactions

In phase III studies, injection site related reactions (e.g. injection site pain, injection site discomfort) were mostly grade 1 or 2 in severity. The incidence of such events was highest in the first 3 months of treatment. In the acromegaly studies, the events were comparable

between pasireotide intramuscular use and octreotide intramuscular use treated patients and were less frequent in inadequately controlled patients compared to medically naïve patients.

QT prolongation

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

Liver enzymes

Transient elevations in liver enzymes have been reported with the use of somatostatin analogues and were also observed in healthy subjects and patients receiving pasireotide in clinical studies. The elevations were mostly asymptomatic, of low grade and reversible with continued treatment. A few cases of concurrent elevations in ALT greater than 3 x ULN and bilirubin greater than 2 x ULN have been observed with the subcutaneous formulation, however not in patients treated with pasireotide intramuscular use. All observed cases of

concurrent elevations were identified within ten days of initiation of treatment. The patients recovered without clinical sequelae and liver function test results returned to baseline values after discontinuation of treatment.

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

Pancreatic enzymes

Asymptomatic elevations in lipase and amylase were observed in patients receiving pasireotide in clinical studies. The elevations were mostly low grade and reversible while continuing treatment.

Pancreatitis is a potential adverse reaction associated with the use of somatostatin analogues due to the association between cholelithiasis and acute pancreatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 32 other – somatostatin and analogues

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatostatin and analogues, ATC code: H01CB05

Mechanism of action:

Pasireotide is a cyclohexapeptide, injectable somatostatin analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somatotropin release inhibiting factor [SRIF]) and other somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors. Five human somatostatin receptor subtypes are known: hsst1, 2, 3, 4, and 5.

These receptor subtypes are expressed in different tissues under normal physiological conditions.

Somatostatin analogues bind to hsst receptors with different

potencies (see Table 2).

Pasireotide binds with high affinity to four of the five hssts.

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

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

Results are the mean±SEM of IC_{50} values expressed as nmol/l.

Pharmacodynamic effects:

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 effective for the treatment of acromegaly.

In vivo studies showed a strong inhibitory effect of pasireotide on GH and IGF-1.

Glucose Metabolism:

In a randomised double blinded mechanism study conducted in healthy volunteers, the development of hyperglycaemia with pasireotide administered as pasireotide subcutaneous use at doses of 0.6 and 0.9 mg twice a day was related to significant decreases in insulin secretion as well as incretin hormones (i.e. glucagon like peptide 1 [GLP 1] and glucose dependent insulinotropic polypeptide [GIP]). Pasireotide did not affect insulin sensitivity.

1.3.1.1.1 Professional Information for medicines for human use

Clinical efficacy and safety:

The efficacy of pasireotide intramuscular use has been demonstrated in two phase III, multicentre studies in acromegaly patients and in one phase III, multicentre study in Cushing's disease patients.

Acromegaly study C2402, inadequately controlled patients

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

Inadequately controlled patients in study C2402 are defined as patients with a mean GH concentration of a 5-point profile over a 2-hour period >2.5 µg/l and sex- and age-adjusted IGF-1 >1.3 × ULN. Patients had to be treated with maximum indicated doses of octreotide intramuscular use (30 mg) or lanreotide deep subcutaneous injection (120 mg) for at least 6 months prior to randomisation. Three-quarters of patients had previously been treated with octreotide intramuscular use and a quarter with lanreotide deep subcutaneous injection. Nearly half of the patients had additional prior medical treatment for acromegaly other than somatostatin analogues. Two-thirds of all patients had undergone prior surgery. Baseline

mean GH was 17.6 µg/l, 12.1 µg/l and 9.5 µg/l, in the 40 mg, 60 mg and active control groups, respectively. IGF-1 mean values at baseline were 2.6, 2.8 and 2.9 x ULN, respectively.

The primary efficacy endpoint was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 µg/l and normalisation of sex- and age-adjusted IGF-1) at week 24 with pasireotide intramuscular use 40 mg or 60 mg versus continued treatment with active control (octreotide intramuscular use 30 mg or lanreotide deep subcutaneous injection 120 mg), separately. The study met its primary efficacy endpoint for both pasireotide intramuscular use doses. The proportion of patients achieving biochemical control was 15.4 % (p-value = 0.0006) and 20.0 % (p-value <0.0001) for pasireotide intramuscular use 40 mg and 60 mg, respectively at 24 weeks compared with zero in the active control arm (Table 3).

Table 3 Key results at week 24 (Study C2402)

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

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

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

The proportion of patients with a reduction or no change in pituitary tumour volume at week 24 was 81.0 % and 70.3 % on pasireotide intramuscular use 40 and 60 mg, and 50.0 % on active control. Furthermore, a higher proportion of patients on pasireotide

intramuscular use (18.5 % and 10.8 % for 40 mg and 60 mg, respectively) than active comparator (1.5 %) achieved a reduction in tumour volume of at least 25 %.

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

Acromegaly study C2305 patients who had no prior medical treatment

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

The two treatment groups were well balanced in terms of baseline demographics and disease characteristics. 59.7 % and 56 % of patients in the pasireotide intramuscular use and octreotide intramuscular use treatment groups, respectively, were patients without

previous pituitary surgery (*de novo*).

The starting dose was 40 mg for pasireotide intramuscular use and 20 mg for octreotide intramuscular use. Dose increase for efficacy was allowed at the discretion of the investigators after three and six months of treatment if biochemical parameters showed a mean GH ≥2.5 µg/l and/or IGF-1 >ULN (age and sex related). Maximum allowed dose was 60 mg for pasireotide intramuscular use and 30 mg for octreotide intramuscular use.

Core phase

The primary efficacy endpoint was the proportion of patients with a reduction of mean GH level to <2.5 µg/l and the normalisation of IGF-1 to within normal limits (age and sex related) at month 12. The primary efficacy endpoint was met; the percentage of patients achieving biochemical control was 31.3 % and 19.2 % for pasireotide intramuscular use and octreotide intramuscular use, respectively, demonstrating a statistically significant superior result favouring pasireotide intramuscular use (p-value = 0.007) (Table 4).

Table 4 Key results at month 12 - phase III study in acromegaly patients)

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

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

ULN = upper limit of normal

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

At month 12, the reduction in tumour volume was comparable between the treatment groups and in patients with and without previous pituitary surgery. The proportion of patients with a

reduction of tumour volume greater than 20 % at month 12 was 80.8% for pasireotide intramuscular use and 77.4 % for octreotide intramuscular use.

Health-related quality of life measured by AcroQol indicated statistically significant improvements in the Physical, Psycholog ups at month 12. Mean improvements from baseline were greater for pasireotide intramuscular use than for octreotide intramuscular use with no statistical significance.

Extension phase

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

During the extension phase, 74 patients continued receiving pasireotide intramuscular use and 46 patients continued with octreotide intramuscular use treatment. At month 25, 48.6% of patients (36/74) in the pasireotide intramuscular use group and 45.7% (21/46) in the octreotide intramuscular use group achieved biochemical control. The percentage of patients who had mean GH values <2.5 µg/l and normalisation of IGF-1 at the same time point was also comparable between the two treatment arms.

During the extension phase, tumour volume continued to decrease.

1.3.1.1.1 Professional Information for medicines for human use

Crossover phase

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

81 patients were crossed over from octreotide intramuscular use to pasireotide intramuscular use, and 38 patients were crossed over from pasireotide intramuscular use to octreotide intramuscular use.

Twelve months after crossover, the percentage of patients achieving biochemical control was 17.3 % (14/81) for pasireotide intramuscular use and 0 % (0/38) for octreotide intramuscular use. The percentage of patients achieving biochemical control, including those patients with IGF-1 <LLN was 25.9 % in the pasireotide intramuscular use group and 0 % in the octreotide intramuscular use group.

Further decrease in tumour volume was observed at month 12 after crossover for both treatment groups and was higher in patients who crossed over to pasireotide intramuscular use (- 24.7 %) than in patients who crossed over to octreotide intramuscular use (-17.9 %).

5.2 Pharmacokinetic properties

Pasireotide for intramuscular use is formulated as microspheres for long-acting release.

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

Absorption:

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 the pamoate complex is predicted to be complete in humans.

Distribution:

In healthy volunteers, pasireotide administered as pasireotide pamoate is widely distributed with a large apparent volume of distribution (Vz/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.

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

Biotransformation:

Pasireotide was shown to be highly metabolically stable in human liver and kidney. microsomes.

1.3.1.1.1 Professional Information for medicines for human use

In healthy volunteers, pasireotide in its unchanged form is the predominant form found in plasma, urine and faeces.

Elimination:

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route.

The apparent clearance (CL/F) of pasireotide administered as the pamoate complex in healthy volunteers is on average 4,5 to 8,5 L/h. Based on population pharmacokinetic (PK) analyses, the estimated CL/F was approximately 5.6 to 8.2 litres/h for typical acromegaly patients.

Steady-state pharmacokinetics:

PK steady state for pasireotide administered as pasireotide pamoate is achieved after three months. Following multiple i.m. doses every 4 weeks (q28d), pasireotide pamoate 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

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

Paediatric patients

1.3.1.1.1 Professional Information for medicines for human use

No studies have been performed in paediatric patients.

Patients with renal impairment

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

Patients with hepatic impairment

Kinetics of pasireotide pamoate have not been studied in subjects with hepatic impairment. In a clinical study for a single subcutaneous dose of pasireotide 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} 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.

Elderly patients (≥65 years)

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

Demographics

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

5.3 Preclinical safety data

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

Pasireotide administered via the subcutaneous route did not affect fertility in male rats but as expected from the pharmacology of pasireotide, females presented abnormal cycles or

acyclicity, and decreased numbers of corpora lutea and implantation sites. Embryo toxicity was seen in rats and rabbits at doses that caused maternal toxicity, but no teratogenic potential was detected. In the pre- and postnatal study in rats, pasireotide had no effects on labour and delivery, but caused slight retardation in the development of pinna detachment and reduced body weight of the offspring.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use, are the responsibility of the user and would normally not be longer than 1 hour at controlled room temperature, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

- Store between 2 to 8 °C.
- Do not freeze.

6.5 Nature and contents of container

SIGNIFOR LA 20 mg 6 ml brownish type I glass vial with a grey flip-off cap

SIGNIFOR LA 40 mg 6 ml brownish type I glass vial with a red flip-off cap

SIGNIFOR LA 60 mg 6 ml brownish type I glass vial with an orange flip-off cap

SIGNIFOR LA SOLVENT: 2 ml solution in 3 ml colourless type I glass pre-filled syringe

Each unit pack contains a blister tray with one injection kit (one vial and, in a separate sealed section, one pre-filled syringe, one vial adapter and one safety-engineered needle (20G x 1.5”) for injection).

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

1.3.1.1.1 Professional Information for medicines for human use

For instructions to use, please refer to section 4.2. ‘Posology and method of administration’.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd.

39 Eleventh Avenue

Hougton Estate, 2198

South Africa

8 REGISTRATION NUMBER(S)

SIGNIFOR LA 20 mg - 49/32/0272

SIGNIFOR LA 40 mg - 49/32/0273

SIGNIFOR LA 60 mg - 49/32/0274

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2017

10 DATE OF REVISION OF TEXT

11 September 2025