NOVARTIS

SANDOSTATIN® LAR® (octreotide acetate)

10 mg, 20 mg, 30 mg powder and solvent for suspension for injection

Professional Information

Document status: Final

Approval date: 05 September 2021

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

SANDOSTATIN® LAR® 10 mg (Dry vial - microspheres for injection)

SANDOSTATIN® LAR® 20 mg (Dry vial - microspheres for injection)

SANDOSTATIN® LAR® 30 mg (Dry vial - microspheres for injection)

SANDOSTATIN® LAR® SUSPENSION VEHICLE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SANDOSTATIN LAR 10 mg: Each vial contains 10 mg octreotide free peptide equivalent to 11,2 mg octreotide acetate.

SANDOSTATIN LAR 20 mg: Each vial contains 20 mg octreotide free peptide equivalent to 22,4 mg octreotide acetate.

SANDOSTATIN LAR 30 mg: Each vial contains 30 mg octreotide free peptide equivalent to 33,6 mg octreotide acetate.

Contains sugar:

SANDOSTATIN LAR powder (amount per vial):

SANDOSTATIN LAR 10 mg: Mannitol 41,0 mg

SANDOSTATIN LAR 20 mg: Mannitol 81,9 mg

SANDOSTATIN LAR 30 mg: Mannitol 122,9 mg

SANDOSTATIN LAR SUSPENSION VEHICLE: Each prefilled syringe contains mannitol 12 mg

SANDOSTATIN LAR suspension contains less than 1 mmol (23 mg) of sodium per dose, i.e. essentially 'sodium-free'.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SANDOSTATIN® LAR® 10 mg:

White to white with yellowish tint powder in a 6 ml colourless glass vial with a grey rubber stopper and a dark blue cap.

SANDOSTATIN® LAR® 20 mg:

White to white with yellowish tint powder in a 6 ml colourless glass vial with a grey rubber stopper and an orange cap.

SANDOSTATIN® LAR® 30 mg:

White to white with yellowish tint powder in a 6 ml colourless glass vial with a grey rubber stopper and a dark red cap.

SANDOSTATIN® LAR® SUSPENSION VEHICLE:

2 ml clear, colourless to slightly yellow or brown solution in a glass syringe (prefilled).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with acromegaly:

- who are adequately controlled on s.c. treatment with a somatostatin analogue
- in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see section 4.2).

Treatment of adult patients with carcinoid tumours with:

- features of the carcinoid syndrome, in whom symptoms are adequately controlled on subcutaneous treatment with octreotide.
- VIPomas

4.2 Posology and method of administration

Posology

SANDOSTATIN LAR SHOULD ONLY BE ADMINISTERED BY DEEP INTRAGLUTEAL INJECTION. The site of repeat intragluteal injections should be alternated between the left and the right gluteal muscle (see *Instructions for use/ handling*).

Acromegaly: *For patients who are adequately controlled with s.c. SANDOSTATIN*, it is recommended to start treatment with the administration of SANDOSTATIN LAR 20 mg at 4-week intervals for 3 months. Treatment with SANDOSTATIN LAR 20 mg can be started on the day after the last dose of s.c. octreotide. Subsequent dosage adjustment should be based on serum growth hormone (GH) and insulin-like growth factor 1/somatomedin C (IGF 1) concentrations and clinical symptoms.

For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF 1) are not fully controlled (GH concentrations still above 2,5 pg/l), the dose may be increased to 30 mg every 4 weeks.

If after 3 months, GH, IGF 1, and/or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks.
For patients whose GH concentrations are consistently below 1 pg/l whose IGF 1 serum concentrations normalised and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg SANDOSTATIN LAR may be administered every 4 weeks. However particularly in this group of patients it is recommended to closely monitor adequate control of serum GH and IGF 1 concentrations and clinical signs/symptoms at this low dose of SANDOSTATIN LAR.

For patients on a stable dose of SANDOSTATIN LAR, assessment of GH and IFG 1 should be made every 6 months.

For patients in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective, a short test dosing period of s.c. administration of octreotide is recommended to assess the response and systemic tolerability of octreotide prior to initiating treatment with SANDOSTATIN LAR as described above.

Carcinoid tumours and VIPomas*: For patients in whom symptoms are adequately controlled with s.c. SANDOSTATIN*, it is recommended to start treatment with the administration of SANDOSTATIN LAR 20 mg at 4-week intervals. The treatment with s.c. SANDOSTATIN should be continued at the previously effective dosage for 2 weeks after the first injection of SANDOSTATIN LAR 20 mg.

For patients who were not previously treated with s.c. SANDOSTATIN, it is recommended to start with the administration of s.c. SANDOSTATIN at a dosage of 0,1 mg three times daily for a short period (approximately 2 weeks) to assess the response and systemic tolerability of octreotide before initiating the treatment with SANDOSTATIN LAR as described above.

For patients in whom symptoms and biological markers are well controlled after 3 months of treatment, the dose may be reduced to 10 mg SANDOSTATIN LAR every 4 weeks.

For patients in whom symptoms are only partially controlled after 3 months of treatment, the dose may be increased to 30 mg SANDOSTATIN every 4 weeks.

For days when symptoms associated with carcinoid tumours may increase during treatment with SANDOSTATIN LAR, additional administration of s.c. SANDOSTATIN is recommended at the dose used prior to the SANDOSTATIN LAR treatment. This may occur mainly in the first 2 months of treatment until therapeutic concentrations of octreotide are reached.

Special populations

Use in elderly patients:

No data is available.

Use in patients with impaired renal function:

No dose adjustment of SANDOSTATIN LAR is necessary.

Use in patients with impaired hepatic function:

No data in patients with impaired hepatic function is available.

Paediatric population

Use in children:

Safety and efficacy of SANDOSTATIN LAR in children aged zero to eighteen years have not been established.

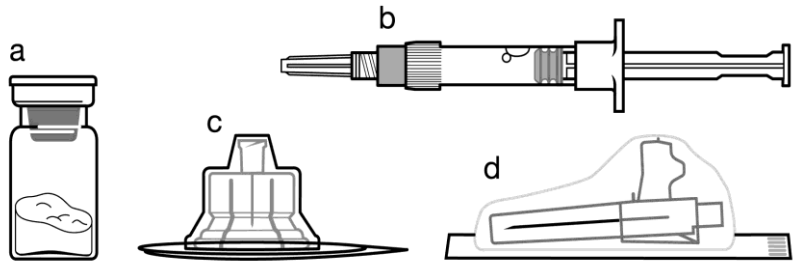
Method of administration

Instructions for use/handling:

Instructions for preparation and intramuscular injection of SANDOSTATIN LAR

FOR DEEP INTRAGLUTEAL INJECTION ONLY

Content:



One vial containing Sandostatin LAR powder
One prefilled syringe containing the vehicle solution for reconstitution
One vial adapter for drug product reconstitution
One 19G x 1.5” safety injection needle

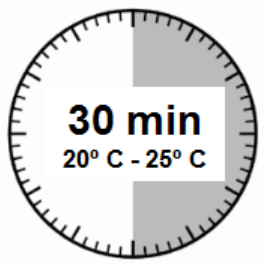
For instructions on preparation of SANDOSTATIN LAR, see section 6.6.

Follow the instructions below carefully to ensure proper reconstitution of SANDOSTATIN LAR before deep intragluteal injection.

The appearance of the constituted suspension of SANDOSTATIN LAR 10 mg, 20 mg or 30 mg, is white to off-white, uniform in appearance and free of agglomerates.

Step 1

Take the Sandostatin LAR injection kit out of the refrigerated storage.

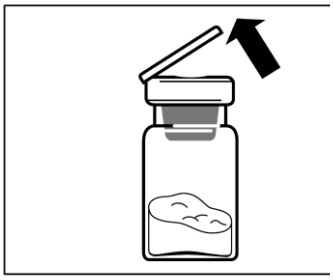


ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

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

Step 2

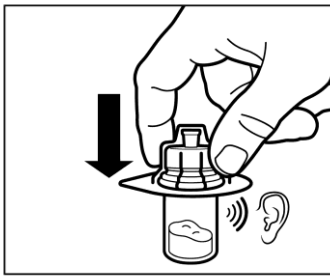
Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol swab.



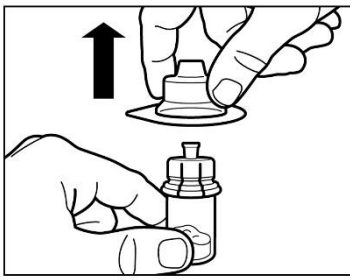
Note: Do not touch the rubber stopper after it has been cleaned.

Peel off the lid film of the blister tray containing the vial adapter. Do NOT remove the vial adapter from the blister tray.

Holding the blister tray, position the vial adapter on top of the vial and push it fully down so that it snaps in place onto the vial, confirmed by an audible "click".

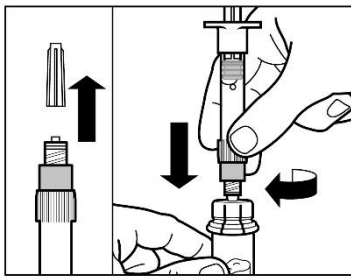


Hold the blister tray by the top and with a vertical movement lift the blister tray off the vial adapter.

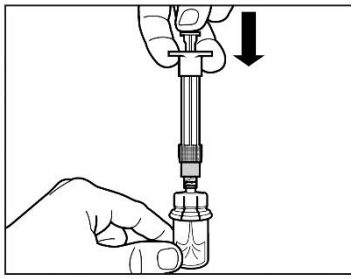


Step 3

Remove the cap from the prefilled syringe containing the vehicle solution and screw the syringe onto the vial adapter.

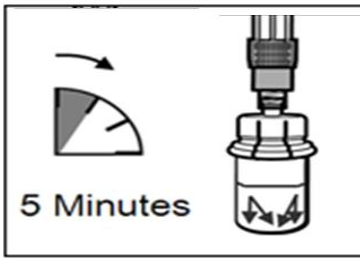


Slowly push the plunger all the way down to transfer all the vehicle solution in the vial.



Step 4

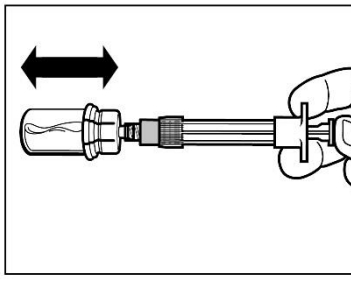
ATTENTION: it is essential to let the vial stand for 5 minutes to ensure that the diluent has fully saturated the powder.



At this stage, prepare the patient for injection.

Note: It is normal if the plunger rod moves up as there might be a slight overpressure in the vial.

Step 5 After the saturation period, make sure the plunger is pushed all the way down in the syringe.



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

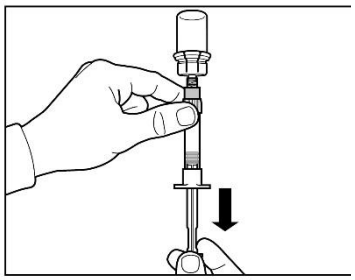
horizontal direction for **a minimum of 30 seconds.**

Check visually that the powder is completely suspended in the vehicle (uniform milky suspension). **Repeat shaking for further 30 seconds if the powder is not completely suspended.**

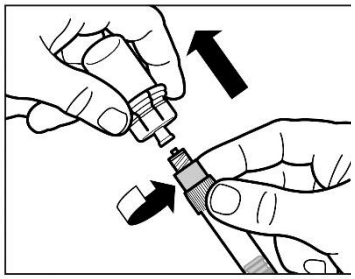
Step 6

Prepare the injection site with an alcohol wipe.

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

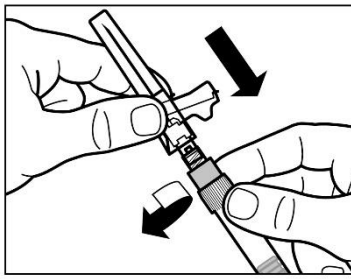


Unscrew the syringe from the vial adapter.



Step 7

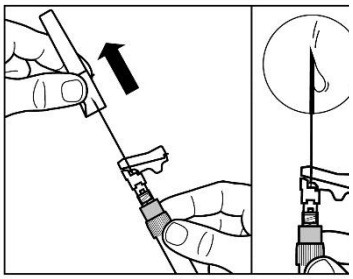
Screw the safety injection needle onto the syringe.



Gently re-shake the syringe to ensure a milky uniform suspension.

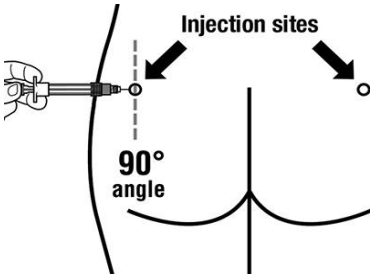
Pull the protective cover straight off the needle.

Gently tap the syringe to remove any visible bubbles and expel them from the syringe. Verify that the injection site has not been contaminated.



Proceed **immediately** to Step 8 for administration to the patient. Any delay may result in sedimentation.

Step 8



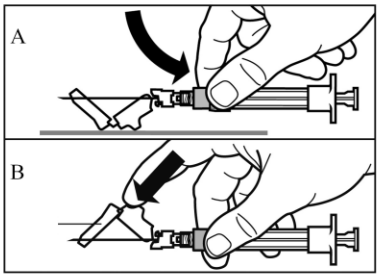
Sandostatin LAR must be given only by deep intragluteal injection, **Never** intravenously.

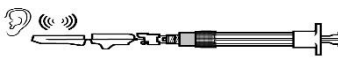
Insert the needle fully into the left or right gluteus at 90º angle to the skin.

Slowly draw back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).

Depress the plunger with steady pressure until the syringe is empty. After completing the injection, withdraw the needle from the injection site and activate the safety guard as shown in **Step 9** below.

Step 9





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

- either by pressing the hinged section of the safety guard down onto a hard surface, (figure A)
- or by pushing the hinge forward with your finger (figure B)

An audible “click” confirms the proper activation.

Dispose of the syringe immediately in a sharps container.

4.3 Contraindications

Known hypersensitivity to octreotide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

As GH-secreting pituitary tumours may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients be carefully monitored. If evidence of tumour expansion appears, alternative procedures are advisable.

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 restore fertility therefore, females of child bearing age should be advised to use effective contraception if necessary during treatment with SANDOSTATIN LAR.

Thyroid function should be monitored in patients receiving prolonged treatment with SANDOSTATIN LAR.

Cardiovascular related events

Cases of bradycardia have been reported. Dose adjustments of medicines such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary.

Gallbladder and related events

Cholelithiasis is a very common event during SANDOSTATIN LAR treatment and may be associated with cholecystitis and biliary duct dilatation (*see section 4.8 Undesirable effects*).

Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients taking Sandostatin in the post-marketing setting. Ultrasonic examination of the gallbladder before and at about 6 monthly intervals during SANDOSTATIN LAR therapy is recommended.

Glucose metabolism

Because of its inhibitory action on growth hormone, glucagon and insulin release, SANDOSTATIN LAR may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with s.c. SANDOSTATIN LAR, in some instances, a state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

In patients with concomitant Type I diabetes mellitus, SANDOSTATIN LAR is likely to affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and Type II diabetics with partially intact insulin reserves, SANDOSTATIN LAR administration may result in post-prandial hyperglycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

In patients with insulinomas, octreotide, because of its greater relative potency in inhibiting the secretion of GH and glucagon than that of insulin, and because of the shorter duration of its inhibitory action on insulin, may increase the depth and prolong the duration of hypoglycaemia. These patients should be closely monitored.

Nutrition

SANDOSTATIN LAR may alter absorption of dietary fats. Depressed vitamin B12 levels and abnormal Schilling's tests have been observed in patients receiving SANDOSTATIN LAR therapy. Monitoring of vitamin B_{12} levels is recommended during therapy with SANDOSTATIN LAR in patients who have a history of vitamin B_{12} deprivation.

Concomitant administration of medicines metabolised by cytochrome P-450 and CYP3A4 should be used with caution as their metabolism may be decreased.

Mannitol Warning:

Patients with the rare hereditary condition of mannitol intolerance should not use SANDOSTATIN LAR.

Sodium content:

Sandostatin LAR contains less than 1 mmol (23 mg) sodium per dose, i.e. is essentially "sodium-free".

4.5 Interaction with other medicines and other forms of Interaction

- Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may be necessary when SANDOSTATIN LAR is administered concomitantly (see section 4.4, Special warnings and precautions for use).
- Dose adjustments of insulin and antidiabetic medicinal products may be required when SANDOSTATIN LAR is administered concomitantly (see section 4.4, Special warnings and precautions for use).
- SANDOSTATIN LAR has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

- Concomitant administration of SANDOSTATIN LAR and bromocriptine increases the bioavailability of bromocriptine.
- Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.
- Concomitant use of radiopharmaceuticals coupled to somatostatin analogues (peptide receptor radionuclide therapy (PRRT)) Somatostatin and its analogues (e.g. octreotide) bind competitively to somatostatin receptors and may impair the efficacy of relevant radiopharmaceuticals (e.g. (177Lu) oxodotreotide). Administration of Sandostatin LAR as a long-acting somatostatin analogue must therefore be interrupted 4-6 weeks before initiation of treatment with PRRT. If required, patients may be treated with short-acting somatostatin analogues up to 24 hours before administration of PRRT.
- Treatment with Sandostatin LAR may be resumed within 4 to 24 hours after administration of PRRT, but must be interrupted once again 4-6 weeks before the radiopharmaceutical is next administered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Female patients of childbearing potential should be advised to use adequate contraception during treatment with SANDOSTATIN LAR.

Pregnancy

Experience with SANDOSTATIN LAR in pregnant or nursing women is limited. Safety in pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience, data on a limited number of exposed pregnancies have been reported in patients with acromegaly, however, in half of the cases the pregnancy outcomes are unknown. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100 to 300 micrograms/day of SANDOSTATIN s.c. or 20 to 30 mg/month of SANDOSTATIN LAR. In approximately two-thirds of the cases with known outcome, the women elected to continue octreotide therapy during their pregnancies. In most of the cases with known outcome, normal newborns were reported but also several spontaneous abortions during the first trimester, and a few induced abortions.

There were no cases of congenital anomalies or malformations due to octreotide usage in the cases that reported pregnancy outcomes.

Studies with SANDOSTATIN in laboratory animals have not shown reproductive toxicological effects of octreotide. A transient growth retardation of offspring was observed in rats, possibly consequent upon the specific endocrine profile of the species tested.

Breastfeeding

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breastfeed during SANDOSTATIN LAR treatment.

Fertility

It is not known whether octreotide has an effect on human fertility. Octreotide did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day.

4.7 Effects on ability to drive and use machines

SANDOSTATIN LAR can cause dizziness, asthenia/fatigue, or headache and may have no or negligible effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with SANDOSTATIN LAR.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions reported during SANDOSTATIN LAR therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with SANDOSTATIN LAR administration were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness, localised pain, biliary sludge, thyroid dysfunction (e.g. decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia and hypoglycaemia.

Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with SANDOSTATIN LAR has led to nutritional deficiency due to malabsorption.

The following adverse drug reactions listed in Table 1 have been accumulated from clinical studies with SANDOSTATIN LAR:

Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: *very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, <1/1000), very rare (<1/10 000),* including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical studies

Endocrine disorders:
Common: Hypothyroidism, thyroid dysfunction (e.g. decreased TSH, decreased Total T4, and decreased Free T4)

Metabolism and nutrition disorders: Very common: Hyperglycaemia Common: Hypoglycaemia, impaired glucose tolerance, anorexia Uncommon: Dehydration
Cardiac disorders: Common: Bradycardia Uncommon: Tachycardia
Respiratory disorders: Common: Dyspnoea
Gastrointestinal disorders: Very common: Diarrhoea, abdominal pain, nausea, constipation, flatulence Common: Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces
Nervous system disorders: Very common: Headache Common: Dizziness
Hepatobiliary disorders: Very common: Cholelithiasis Common: Cholecystitis, biliary sludge, hyperbilirubinaemia
Skin and subcutaneous tissue disorders: Common: Pruritus, rash, alopecia
General disorders and administration site conditions: Very common: Injection site localized pain Common: Asthenia

Investigations: Common: Elevated transaminase levels

Post-marketing:

Spontaneously reported adverse reactions' presented in Table 2, are reported voluntarily and it is not possible to reliably establish frequency or a causal relationship to drug exposure.

Table 2: Adverse drug reactions derived from spontaneous reports

Blood and lymphatic system disorders: Thrombocytopenia
Immune disorders: Anaphylaxis, allergy/hypersensitivity reactions, rash.
Skin and subcutaneous tissue disorders: Urticaria
Hepatobiliary disorders: Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.
Cardiac disorders: Dysrhythmias
Investigations: Increased alkaline phosphatase levels, increased gamma glutamyl transferase.

Description of selected adverse reactions

Gastrointestinal disorders and nutrition

In instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding.

Gallbladder and related reactions

Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge (*see section 4.4 Special warnings and precautions for use*).

Development of gallstones has been reported in 15 to 30 % of long-term recipients of s.c. SANDOSTATIN.

The prevalence in the general population (aged 40 to 60 years) is about 5 to 20 %. Long-term exposure to SANDOSTATIN LAR of patients with acromegaly or gastro-entero-pancreatic tumors suggests that treatment with SANDOSTATIN LAR does not increase the incidence of gallstone formation, compared with s.c. treatment.

Pancreatitis

Instances of acute pancreatitis have been reported within the first hours or days of s.c. SANDOSTATIN treatment. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long- term s.c. SANDOSTATIN treatment.

Thrombocytopenia

Thrombocytopenia has been reported during post-marketing experience, particularly during treatment with SANDOSTATIN (i.v.) in patients with cirrhosis of the liver, and during treatment with SANDOSTATIN LAR. This is reversible after discontinuation of treatment.

Cardiac disorders

In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarisation, low voltage, RJS transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to SANDOSTATIN LAR is however not established because many of these patients have underlying cardiac diseases (*see section 4.4 Special warnings and precautions for use*).

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The adverse events reported were hot flushes, dysrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

The management of overdosage is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code:

Somatostatin and analogues, ATC code: H01CB02

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a prolonged duration of action. It inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

Octreotide has been shown to inhibit:

• Release of growth hormone (GH) stimulated by arginine, exercise and insulin-induced hypoglycaemia.

• Post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP system, and arginine-stimulated release of insulin and glucagon.

• Thyrotropin-releasing hormone (TRH) stimulated release of thyroid-stimulating hormone (TSH).

Octreotide inhibits GH preferentially over insulin.

In previously untreated acromegaly patients with GH-secreting pituitary adenoma, long acting octreotide treatment resulted in a tumour volume reduction of > 20 % in a significant proportion (50 %) of patients.

5.2 Pharmacokinetic properties

Absorption:

After single i.m. injections of long acting octreotide, the serum octreotide concentration reaches an initial peak within 1 hour after administration, followed by a progressive decrease to a low undetectable octreotide level within 24 hours. After this peak on day 1, octreotide remains at sub-therapeutic levels in the majority of the patients for the following 7 days. Thereafter, octreotide concentrations increase again, and reach plateau concentrations at around day 14 and remain relatively constant during the following 3 to 4 weeks. The peak level during day 1 is lower than levels during the plateau phase, and no more than 0,5 % of the total medicine occurs during day 1. After about day 42, the octreotide concentration decreases slowly, concomitant with the terminal degradation phase of the polymer matrix of the dosage form.

In patients with acromegaly, mean plateau octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg of octreotide amount to 358 ng/l, 926 ng/l, and 1 710 ng/l, respectively. Steady-state serum octreotide concentrations, reached after 3 injections at 4-week intervals, are higher by a factor of approximately 1,6 to 1,8 and amount to 1 557 ng/l, and 2 384 ng/l after multiple injections of 20 mg and 30 mg of octreotide, respectively.

No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a duration of up to 28 monthly injections of octreotide.
The pharmacokinetic profile of octreotide after injection of octreotide reflects the release profile from the polymer matrix and its biodegradation.

Distribution:

Once released into the systemic circulation, octreotide distributes according to its known pharmacokinetic properties, as described for s.c. administration. The volume of distribution of octreotide at steady state is 0,27 l/kg and the total body clearance is 160 ml/min. Plasma protein binding amounts to 65 % and essentially no drug is bound to blood cells.

Biotransformation/Elimination:

Most of the peptide is eliminated via the feces, while some is excreted unchanged into the urine.

Linearity:

In patients with carcinoid tumours, the mean (and median) steady-state serum concentrations of octreotide after multiple injections of 10 mg, 20 mg, and 30 mg of octreotide given at 4-week intervals also increased linearly with dose and were 1 231 (894) ng/l, 2 620 (2270) ng/l, and 3 928 (3010) ng/l, respectively.

5.3 Preclinical safety data

Genotoxicity

Octreotide and/or its metabolites were devoid of mutagenic potential when investigated *in vitro* in validated bacterial and mammalian cell test systems. In one study, an increased frequency of chromosomal changes were observed in V79 Chinese hamster cells, albeit at high and cytotoxic concentrations only. Chromosomal aberrations were however not increased in human lymphocytes incubated with octreotide acetate.

Carcinogenicity/Chronic toxicity

The 116 week carcinogenicity study in rats with s.c. SANDOSTATIN also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest s.c. dose level of 1.25 mg/kg per day. The finding was associated with an increased incidence of endometritis, a decreased number of ovarian corpora lutea, a reduction in mammary adenomas and the presence of uterine glandular and luminal dilation, suggesting a state of hormonal imbalance. The available information clearly indicates that the findings of endocrine-mediated tumors in rats are species-specific and are not relevant for the use of the drug in humans.

Reproductive toxicity

Reproduction studies have been performed with SANDOSTATIN in rats and rabbits at parenteral doses of up to 1 mg/kg body weight per day. Some retardation of the physiological growth was noted in the offspring of rats which was transient and most likely attributable to GH inhibition brought about by excessive pharmacodynamic activity. There

was no evidence of teratogenic, embryo/fetal or other reproduction effects due to octreotide.

The microspheres were devoid of reproductive toxicological effects when tested in standard studies for reproductive toxicity in rats and rabbits

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder (vial):

- Poly(DL)-lactide-co-glycolide
- Mannitol, sterilised.

SANDOSTATIN suspension vehicle - Solvent (Prefilled syringe):

- Carmellose sodium
- Mannitol (E421)
- 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

3 years.

The product must not be stored after reconstitution (must be used immediately).

6.4 Special precautions for storage

Store at 2 ℃ to 8 ℃, (in a refrigerator).

Store in the original package/container.

Keep vial in the outer carton in order to protect it from light.

SANDOSTATIN® LAR® can remain below 25 ℃ on the day of the injection. The suspension, however, must only be prepared immediately prior to i.m. injection.

SANDOSTATIN® LAR® is a single dose vial and any unused portion must be discarded.

6.5 Nature and contents of container

Cardboard box containing:

One glass vial containing: microspheres for injection.

One glass prefilled syringe containing: vehicle for parenteral use.

One vial adapter for drug product reconstitution.

One 19G x 1.5 inch safety injection needle.

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.

Preparation of the reconstituted suspension

There are 3 critical actions in the reconstitution of SANDOSTATIN 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, **ensure that the powder is fully saturated** by letting the vial stand for 5 minutes.

After saturation, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until a uniform suspension is formed.** The SANDOSTATIN LAR suspension must only be prepared **immediately** before administration.

SANDOSTATIN LAR should only be administered by a trained healthcare professional.

The appearance of the constituted suspension of SANDOSTATIN LAR 10 mg, 20 mg or 30 mg, is white to off-white, uniform in appearance and free of agglomerates.

7. THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg 2090

8. REGISTRATION NUMBER(S)

SANDOSTATIN® LAR® 10 mg: 33/34/0239

SANDOSTATIN® LAR® 20 mg: 33/34/0240

SANDOSTATIN® LAR® 30 mg: 33/34/0241

SANDOSTATIN® LAR® SUSPENSION VEHICLE: 33/34/0242

9. DATE OF FIRST AUTHORISATION

28 August 2000

10 DATE OF REVISION OF TEXT

05 September 2021

	Namibia		Botswana	
SANDOSTATIN® LAR® 10 mg:	08/34/0127	NS2	BOT1001717	S2
SANDOSTATIN® LAR® 20 mg:	04/34/1418	NS2	BOT1001715	S2
SANDOSTATIN® LAR® 30 mg:	08/34/0128	NS2	BOT1001714	S2
SANDOSTATIN® LAR® SUSPENSION VEHICLE	04/34/1417	NS2		