1 Trade name(s)

SANDOSTATIN® LAR® 10 mg* powder and solvent for suspension for injection.

SANDOSTATIN® LAR® 20 mg powder and solvent for suspension for injection.

SANDOSTATIN® LAR® 30 mg powder and solvent for suspension for injection.

2 Description and composition

Pharmaceutical form(s)

Powder and solvent for suspension for injection.

Kit with vial adapter and safety needle:

Powder: white to off-white powder.

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

Sandostatin® LAR® is a long-acting depot injection form of octreotide. Powder (microspheres for suspension for injection) to be suspended in a vehicle immediately prior to i.m. injection.

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

Active substance(s)

The active substance is octreotide free peptide. 10 mg*, 20 mg or 30 mg nominally 4.15% of fill weight equivalent to 4.65% of octreotide acetate.

Excipients

Vial

Poly (DL-lactide-co-glycolide) 78.35% of nominal fill weight; sterile mannitol 17.0% of nominal fill weight.

Prefilled syringe

Kit with vial adapter and safety needle:

One **prefilled syringe** (solvent for parenteral use), containing: sodium carboxymethylcellulose (14 mg), mannitol (12 mg), poloxamer 188 (4 mg); water for injection qs ad 2 mL.

3 Indications

Treatment of patients with acromegaly:
- Who are adequately controlled on s.c. treatment with Sandostatin
- *In whom* surgery, radiotherapy or dopamine agonist treatment is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see Dosage regimen and administration)

Relief of symptoms associated with gastro-entero-pancreatic endocrine tumors:
- Carcinoid tumors with features of the carcinoid syndrome
- VIPomas
- Glucagonomas

Treatment of patients with advanced Neuroendocrine Tumors of the midgut.

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4 Dosage regimen and administration

Sandostatin LAR may only be administered by deep intragluteal injection. The site of repeat intragluteal injections should be alternated between the left and right gluteal muscle (see section Instructions for use and handling).

Dosage regimen

General target population

Acromegaly

Patient who are adequately controlled with subcutaneous Sandostatin

It is recommended to start treatment with the administration of 20 mg Sandostatin LAR at 4-week intervals for 3 months. Patients on treatment with s.c. Sandostatin can start treatment with Sandostatin LAR can be started on the day after the last dose of s.c. Sandostatin. 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 2.5µg/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 µg/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. In order to permit successful endocrine testing of the completeness of tumour removal 5-6 weeks post-surgery, the last injection of Sandostatin LAR should be administered at least 3-4 weeks prior to surgery.

For patients on a sustained, unchanging dose of Sandostatin LAR, assessment of GH and IGF-1 should be made every 6 months.

Patient not previously treated with subcutaneous Sandostatin

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

Gastro-entero-pancreatic endocrine tumors

Treatment of patients with symptoms associated with functional gastro-entero-pancreatic neuroendocrine tumors

Patient who are adequately controlled with subcutaneous Sandostatin

It is recommended to start treatment with the administration of 20 mg Sandostatin LAR at 4-week intervals. Patient on treatment with s.c. Sandostatin should continue at the previously effective dosage for 2 weeks after the first injection of Sandostatin LAR. Response should be assessed after 3 months of treatment.

Patient not previously treated with subcutaneous 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.

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Treatment of patients with advanced Neuroendocrine Tumors of the midgut

The recommended dose of Sandostatin LAR is 30 mg administered every 4 weeks (see section Pharmacodynamics). Treatment with Sandostatin LAR for tumour control should be continued in the absence of tumour progression.

Dose titration:

For patients in whom symptoms and biological markers are well controlled after three 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 LAR every 4 weeks.

For days when symptoms associated with gastro-entero-pancreatic tumors 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

Renal impairment

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered s.c. as Sandostatin. Therefore, no dose adjustment of Sandostatin LAR is necessary.

Hepatic impairment

In a study with Sandostatin administered s.c. and i.v. it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. Due to the wide therapeutic window of octreotide, no dose adjustment of Sandostatin LAR is necessary in patients with liver cirrhosis.

Pediatric patients (below 18 years)

There is very limited experience with the use of Sandostatin LAR in children.

Geriatric patients (65 years or above)

In a study with Sandostatin administered s.c., no dose adjustment was necessary in patients ≥ 65 years of age. Therefore, no dose adjustment is necessary in this group of patients with Sandostatin LAR.

4 Contraindications

Known hypersensitivity to octreotide or to any of the excipients (see section Description and composition).

5 Warnings and precautions

General

As GH-secreting pituitary tumors 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 normalization 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 octreotide (see also section Pregnancy, breast-feeding and fertility).

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

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Cardiovascular related events

Cases of bradycardia have been reported (frequency: common). Dose adjustments of drugs 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 treatment and may be associated with cholecystitis and biliary duct dilatation (see section Adverse drug reactions). Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients taking Sandostatin LAR 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, in some instances, a state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycemia 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 s.c. administration may result in increases in post-prandial glycaemia. 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

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin LAR in patients who have a history of vitamin B12 deprivation.

6 Interactions

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 Warnings and precautions).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin LAR is administered concomitantly (see section Warnings and precautions).

Octreotide has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Concomitant administration of octreotide and bromocriptine increases the bioavaibility of bromocriptine.

Limited published data indicate that somatostatin analougues might decrease the metabolic clearance of of compounds known to be metabolised by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that ocreotide may have this effect, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic indix (e.g. quinidine, terfenadine) should therefore be used with caution.

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7 Pregnancy, breast-feeding and fertility

Pregnancy

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 (see section Non-clinical safety data).

Sandostatin should only be prescribed to pregnant women under compelling circumstances (see also section Warnings and precautions).

Breast-feeding

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during Sandostatin 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 (see section Non-clinical safety data).

Effects on ability to drive and use machines

No data exist on the effects of Sandostatin LAR on the ability to drive and use machines.

8 Adverse drug reactions

Summary of the safety profile

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

The most commonly reported adverse reactions in clinical trials with octreotide administration were diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycemia and constipation. Other commonly reported adverse reactions were dizziness, localized 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 hypoglycemia.

Intermittent gastrointestinal side effects resembling acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding can occur in about 10% of patients, but usually decline with continued treatment.

The following adverse drug reactions, listed in Table-1, have been accumulated from clinical studies with octreotide:

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Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table-1 Adverse drug reactions reported in clinical studies

Endocrine disorders	
Common:	Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased Total T4, and decreased Free T4).
Metabolism and nutrition disorders	
Very common:	Hyperglycaemia.
Common:	Hypoglycaemia, glucose tolerance impaired, decreased appetite.
Uncommon:	Dehydration.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Cardiac disorders	
Common:	Bradycardia.
Uncommon:	Tachycardia.
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea.
Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence.
Common:	Dyspepsia, vomiting, abdominal distention, steatorrhoea, loose stools, faeces discoloured.
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 reaction.
Common:	Asthenia.
Investigations	
Common:	Transaminase increased.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Sandostatin LAR via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

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Table-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders Thrombocytopenia.
Immune disorders Anaphylactic reaction, allergy/hypersensitivity reactions.
Cardiac disorders Arrhythmias.
Hepatobiliary disorders Pancreatitis acute, acute hepatitis without cholestasis, hepatitis cholestatic, cholestasis, jaundice, jaundice cholestatic.
Skin and subcutaneous tissue disorders Urticaria.
Investigations Blood alkaline phosphatase increased, gamma glutamyl transferase increased.

Description of selected adverse drug reactions

Gastrointestinal disorders and nutrition

In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Although measured fecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption.

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. 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. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Pancreatitis

Cholelithiasis-induced pancreatitis has been reported for patients on long-term Sandostatin s.c. treatment. In very rare instances, acute pancreatitis has been reported within the first hours or days of Sandostatin s.c. treatment and resolved on withdrawal of the drug.

Cardiac disorders

Bradycardia is a common adverse reaction with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see section Warnings and precautions).

Hypersensitivity and anaphylactic reactions

Hypersensitivity and allergic reactions have been reported during post-marketing. When these occur, they mostly affect the skin, rarely the mouth and airways. Isolated cases of anaphylactic shock have been reported.

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Injection site reactions

Injection site reactions include pain, redness, haemorrhage, pruritus, swelling or induration, which have been reported in patients receiving Sandostatin LAR. However, these events did not require any clinical intervention in the majority of the cases.

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.

9 Overdosage

A limited number of accidental overdoses of Sandostatin LAR have been reported. The doses ranged from 100 mg to 163 mg/month of Sandostatin LAR. The only adverse event reported was hot flushes.

Cancer patients receiving doses of Sandostatin LAR up to 60 mg/month and up to 90 mg/2 weeks have been reported. These doses were in general well tolerated; however, the following adverse events have been reported: frequent urination, fatigue, depression, anxiety, and lack of concentration.

The management of overdosage is symptomatic.

10 Clinical Pharmacology

Pharmacotherapeutic group: anti-growth hormone, ATC code: H01CB02.

Mechanism of action (MOA)

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably 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.

In *animals*, octreotide is a more potent inhibitor of GH, glucagon and insulin release than somatostatin, with greater selectivity for GH and glucagon suppression.

In *healthy subjects* octreotide, like somatostatin, has been shown to inhibit

- release of 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,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH)

Pharmacodynamics (PD)

Unlike somatostatin, octreotide inhibits GH preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. GH in patients with acromegaly).

In ***patients with acromegaly***, Sandostatin LAR, a galenical formulation of octreotide suitable for repeated administration at intervals of 4 weeks, delivers consistent and therapeutic octreotide serum concentrations thus consistently lowering GH and normalising IGF 1 serum concentrations in the majority of patients. In most patients, Sandostatin LAR markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paraesthesia, fatigue, *osteo*arthralgia and carpal tunnel syndrome.

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

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For *patients with functional tumors of the gastro-entero-pancreatic endocrine system*, treatment with Sandostatin LAR provides continuous control of symptoms related to the underlying disease. The effect of octreotide in different types of gastro-entero-pancreatic tumors are as follows:

Carcinoid tumors

Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5 hydroxyindole acetic acid.

VIPomas

The biochemical characteristic of these tumors is overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of octreotide results in alleviation of the severe secretory diarrhoea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalaemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. In some patients, computer tomography scanning suggests a slowing or arrest of progression of the tumour, or even tumour shrinkage, particularly of hepatic metastases. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of on the state of mild diabetes mellitus which frequently occurs is not marked and, in general, does not result in a reduction of requirements for insulin or oral hypoglycaemic agents. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of often leads to an immediate reduction in plasma glucagon levels, this decrease is generally not,maintained over a prolonged period of administration, despite continued symptomatic improvement.

Pharmacokinetics (PK)

After single i.m. injections of Sandostatin LAR the serum octreotide concentration reaches a transient initial peak within 1 hour after administration, followed by a progressive decrease to allow 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, reach plateau concentrations at around day 14 and remain relatively constant during the plateau phase, and no more than 0.5% of the total drug release 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 patient with acromegaly, mean plateau octreotide concentrations after single doses of 10 mg*, 20 mg, and 30 mg of sandostatin LAR amount to 358 ng/L, 926 ng/L and 1710 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 1557 ng/L, and 2384 ng/L after multiple injections of 20 mg and 30 mg of Sandostatin LAR, respectively.

In patients with carcinoid tumors, the mean (and median) steady state serum concentrations of octreotide after multiple injections of 10 mg*, 20 mg, 30 mg of Sandostatin LAR given at 4-week intervals also increased linearly with dose and were 1231 (894) ng/L, 2620 (2270) ng/L, and 3928 (3010) ng/L, respectively.

No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR.

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The pharmacokinetic profile of octreotide after injection of Sandostatin LAR reflects the release profile from the polymer matrix and its biodegradation. Once released into the systemic circulation, octreotide distributes according to its known pharmacikinetic 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.

11 Clinical studies

Acromegaly

Two dose finding studies (SMSC 201-E-01 and SMSC 202-E-00) were initially carried out with Sandostatin LAR in acromegalic patients. These studies were prospective single dose, double-blind, randomized, multi-centre studies designed to assess the following doses of Sandostatin LAR injected intramuscularly: 10, 20 and the 30 mg.

Patients who showed GH suppression on t.i.d. Sandostatin s.c. pre-treatment were selected for these studies. Out of the 93 patients included, 78 were "responders" (mean 12- hour GH serum concentrations below 5 µg/L during pre-treatment with Sandostatin s.c.) and 15 patients were "partial responders" to Sandostatin s.c. (GH mean concentrations suppressed to approximately 50% of pretreatment levels but not to below 5 µg/L).

The primary efficacy parameter was the mean 12-hour GH serum concentrations. The results of the double-blind studies SMSC 201-E-01 and SMSC 202-E-00 showed that the 20 and 30 mg doses of Sandostatin LAR are able to suppress GH levels below 5µg/L from day 14 until day 42. The i.m. injection was well tolerated locally and the adverse events analysis reflected the known gastro-intestinal reactions to octreotide.

To document the long-term tolerability, safety and efficacy of Sandostatin LAR in acromegalic patients, three prospective open-label extensions for each of the two double-blind studies were completed (SMSC 201-E-02/-03/-04 and SMSC 202-E-01/-02/-03).

All patients that had participated to studies SMSC 201-E-01 and SMSC 202-E-00 and had well tolerated the study drug were offered to continue treatment with additional injections of Sandostatin LAR in the open label extension studies. A total of 101 patients entered these studies and 87 completed all extensions, thus receiving 28 injections of Sandostatin LAR.

Investigators were allowed to titrate patients to their optimal therapeutic response (using 10, 20, 30 or exceptionally 40 mg doses). An interval of 28 days between injections was considered optimal for providing consistent steady-state concentrations of octreotide, based on pharmacokinetic simulation of single dose profiles and considering the linearity of pharmacokinetics of octreotide. The primary efficacy endpoint in the extension studies was the 8-hours GH serum concentrations.

These extension studies demonstrated that long-term treatment of acromegalic patients with Sandostatin LAR administered at doses of 10-30 mg i.m. in patients known to be responsive to Sandostatin s.c. results in a sustained suppression of mean 8-hour GH levels throughout the dosing interval. These effects were accompanied by a marked reduction in IGF-I concentrations and a persistent regression of the symptoms of acromegaly.

Long-term systemic tolerability of Sandostatin LAR was good, the pattern, severity and duration of adverse events was similar to those historically reported for the s.c. treatment with Sandostatin and for short-term treatment with Sandostatin LAR.

GEP tumors

The clinical trial program for Sandostatin LAR in GEP tumors consisted of one controlled clinical study (SMSE 351) which was carried out in patients with malignant carcinoid syndrome symptomatically controlled by Sandostatin s.c.

Study SMSE351 was a randomized, double-blind, multicenter prospective study of efficacy, safety and tolerability of multiple dose levels of Sandostatin LAR (10, 20 and 30 mg doses) administered at 4-week interval versus open-label subcutaneous Sandostatin. Ninety-three patients were enrolled and 80 completed the study.

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Assessment of treatment success, partial treatment success or treatment failure was based on the degree and duration of suppression of carcinoid symptoms as indicated by the need for rescue therapy with Sandostatin in patients randomized to one of the Sandostatin LAR groups, or by the need for an increase in dosage in patients randomized to the Sandostatin group, at the end of Week 20 and Week 24.

A level of efficacy comparable to that achieved with Sandostatin s.c. was observed with Sandostatin LAR after the 5th and 6th injections at Weeks 20 and 24 respectively, and at endpoint (see Table 3).

Table-3 Summary of treatment success in Study SMSE 351 (Intent To Treat population)

Visit	Treatment outcome	Sandostatin s.c. n (%)	Sandostatin LAR 10 mg* n (%)	Sandostatin LAR 20 mg n (%)	Sandostatin LAR 30 mg n (%)
Week 20	N	26	19	16	23
	Success	16 (61.5)	12 (63.2)	10 (62.5)	14 (60.9)
	Part. Success	1 (3.8)	2 (10.5)	1 (6.3)	-
Week 24	N	26	19	15	21
	Success	14 (53.8)	12 (63.2)	9 (60.0)	13 (61.9)
	Part. Success	1 (3.8)	-	1 (6.7)	1 (4.8)
Endpoint	N	26	22	20	25
	Success	14 (53.8)	12 (54.5)	9 (45.0)	13 (52.0)
	Part. Success	1 (3.8)	-	1 (5.0)	1 (4.0)

Success = no need for rescue Sandostatin s.c or increased s.c dosage

Part. Success = need for rescue Sandostatin s.c or increased s.c dosage on no more than 2 occasions during the preceding 4 weeks for a total of 5 days or less.

Endpoint = last not missing post-baseline evaluation

The data recorded in Study SMSE 351 showed that Sandostatin LAR is as effective and as well tolerated as Sandostatin s.c. injections in the treatment of patients with carcinoid symptoms.

Advanced Neuroendocrine Tumors of the midgut

A Phase III, randomized, double-blind, placebo-controlled study (PROMID) demonstrated that Sandostatin LAR inhibits tumor growth in patients with advanced Neuroendocrine Tumors of the midgut.

85 patients were randomized to receive Sandostatin LAR 30 mg every 4 weeks (n = 42) or placebo (n = 43) for 18 months, or until tumor progression or death.

Main inclusion criteria were: treatment naïve; histologically confirmed; locally inoperable or metastatic well-differentiated; functionally active or inactive neuroendocrine tumors/carcinomas; with primary tumor located in the midgut believed to be of midgut origin if a primary within the pancreas, chest, or elsewhere was excluded.

The primary endpoint was time to tumor progression or tumor-related death (TTP) based on central radiological review using WHO criteria.

In the intent-to-treat analysis population (ITT) (all randomised patients), 26 and 41 progressions or tumour-related deaths were seen in the Sandostatin LAR and placebo groups, respectively (HR = 0.32; 95% CI, 0.19 to 0.55; p-value = 0.000015).

In the conservative ITT (cITT) analysis population in which 3 patients were censored at randomization, 26 and 40 progressions or tumour-related deaths were observed in the Sandostatin LAR and placebo groups, respectively (HR=0.34; 95% CI, 0.20 to 0.59; p-value = 0.000072; Fig 1). Median time to tumour progression was 14.3 months (95% CI, 11.0 to 28.8 months) in the Sandostatin LAR group and 6.0 months (95% CI, 3.7 to 9.4 months) in the placebo group.

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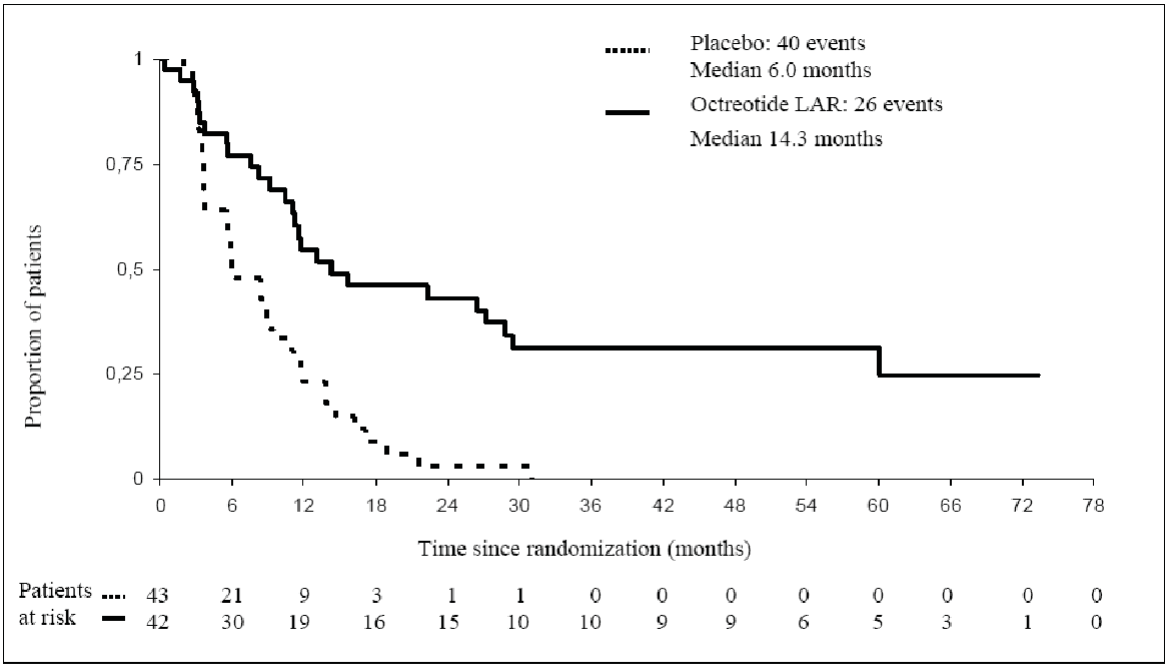
In the per-protocol analysis population (PP) in which additional patients were censored at end study therapy, tumour progression or tumour-related death was observed in 19 and 38 Sandostatin LAR and placebo recipients, respectively (HR = 0.24; 95% CI, 0.13 to 0.45; p-value = 0.0000036).

Figure 1 **Kaplan-Meier estimates of TTP comparing Sandostatin LAR with placebo (conservative ITT population)**



Logrank test stratified by functional activity: P=0.000072, HR= 0.34 [95%-CI: 0.20–0.59]

Table-4 **TTP results by analysis populations**

	TTP Events		Median TTP months [95% C.I.]		HR [95% C.I.] p-value *
	Sandostatin LAR	Placebo	Sandostatin LAR	Placebo	
ITT	26	41	NR	NR	0.32 [95% CI, 0.19 to 0.55] P=0.000015
cITT	26	40	14.3 [95% CI, 11.0 to 28.8]	6.0 [95% CI, 3.7 to 9.4]	0.34 [95% CI, 0.20 to 0.59] P=0.000072
PP	19	38	NR	NR	0.24 [95% CI, 0.13 to 0.45] P=0.0000036

NR=not reported; HR=hazard ratio; TTP=time to tumour progression; ITT=intention to treat; cITT=conservative ITT; PP=per protocol
*Logrank test stratified by functional activity

P-value is two sided and is significant at the 0.0122 level.

Log-rank and Cox are stratified by functioning tumor at randomization, as documented on the CRF.

Treatment effect was similar in patients with functionally active (HR = 0.23; 95% CI, 0.09 to 0.57) and inactive tumors (HR = 0.25; 95% CI, 0.10 to 0.59).

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After 6 months of treatment, stable disease was observed in 67% of patients in the Sandostatin LAR group and 37% of patients in the placebo group.

Based on the significant clinical benefit of Sandostatin LAR observed in this pre-planned interim analysis the recruitment was stopped.

The safety of Sandostatin LAR in this trial was consistent with its established safety profile.

13 Non-clinical safety data

Repeat dose toxicity

In two repeated dose studies performed in rats by i.m. injection of 2.5 mg Sandostatin LAR in 50-mg microspheres every 4 weeks for 21/24 weeks, no drug-related necropsy findings were observed. The only histopathological findings considered to be of significance were at the injection site in treated and control animals, where the microspheres had provoked a reversible granulomatous myositis.

Genotoxicity

Sandostatin administered s.c. 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 frequencies of chromosomal changes were observed in V79 Chinese hamster cells *in vitro*, albeit at high and cytotoxic concentrations only. Chromosomal aberrations were however not increased in human lymphocytes incubated with octreotide acetate. *In vivo*, no clastogenic activity was observed in the bone marrow of mice treated with octreotide i.v. (micronucleus test) and no evidence of genotoxicity was obtained in male mice using a DNA repair assay on sperm heads. The microspheres were devoid of mutagenic potential when tested in standard assays for genotoxicity.

Carcinogenicity/chronic toxicity

In studies in rats in which s.c. Sandostatin at daily doses up to 1.25 mg/kg body weight were administered, fibrosarcomas were observed, predominantly in a number of male animals, at the s.c. injections site after 52, 104 and 113/116 weeks. Local tumors accured also in the control rats, however development of these tumors was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enchanced by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were observed neither in mice receiving daily s.c. injections of Sandostatin at doses up to 2 mg/kg for up to 99 weeks, nor in dogs which were treated with daily s.c. doses of the drug for 52 weeks.

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 findings 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 drugs in humans.

Reproduction toxicity

Reproduction studies have been performed 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.

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14 Pharmaceutical information

Incompatibilities

Sandostatin LAR microspheres for injection is to be used as a single dose containers, without any dilution with other products. Therefore, no compatibility data with other products have been generated.

Special precautions for storage

Store at 2 °C to 8°C (in a refrigerator), protect from light. Do not freeze. Sandostatin LAR can remain at room temperature on the day of injection. Do not store Sandostatin LAR above 25°C during a period of approx. 24 hour prior to injection. The suspension, however, must not be prepared until immediately before injection. Sandostatin LAR should be kept out of the reach of children.

Shelf-life

The expiry date is indicated on the packaging.

Nature and content of container

Kit with vial adapter and safety needle:

The microspheres are packaged in 6-mL glass vial, with a fluoroelastomer-coated rubber stopper and sealed with an aluminium flip-off seal.

The vehicle is packaged in the prefilled glass syringe which is closed with two rubber stoppers (a font and a plunger stopper).

Vial adapter:

One safety injection needle [40mm (1.5 inch), 19 Gauge].

Special precautions for disposal

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

Instruction for use and handling

See the instructions located at the end of this leaflet.

HARUS DENGAN RESEP DOKTER

PACKAGE QUANTITIES AND REGISTRATION NUMBER

Pack Sizes :

Kit with vial adapter and safety needle:
Dus, vial 6 ml @ 625 mg serbuk injeksi + 1 pre-filled syringe @ 2 ml pelarut + 1 vial adapter + 1 safety injection needle
Sandostatin LAR 20 mg Reg. No. DKI0567505144B1

Dus, vial 6 ml @ 900 mg serbuk injeksi + 1 pre-filled syringe @ 2 ml pelarut + 1 vial adapter + 1 safety injection needle
Sandostatin LAR 30 mg Reg. No. DKI0567505144C1

Manufactured by Sandoz GmbH, Langkampfen, Austria for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

**Disclaimer: Sandostatin LAR 10 mg is not registered and marketed in Indonesia*

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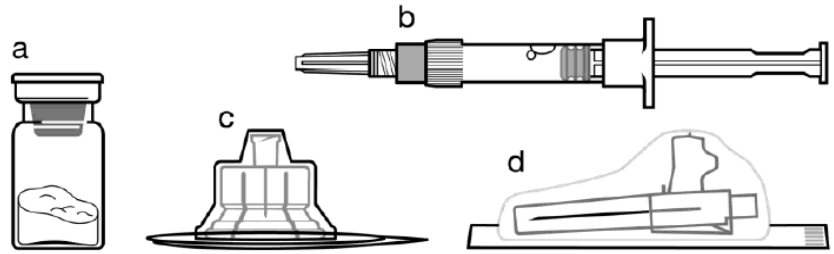
Kit with vial adapter and safety needle

Instructions for intramuscular injection of Sandostatin LAR

FOR DEEP INTRAGLUTEAL INJECTION ONLY

Content:



a One vial containing Sandostatin LAR powder
b One prefilled syringe containing the vehicle solution for reconstitution
c One vial adapter for drug product reconstitution
d One safety injection needle

Follow the instructions below carefully to ensure complete saturation of the powder and its uniform suspension before i.m. injection.

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 health professional.

Step 1

- Remove the Sandostatin 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.

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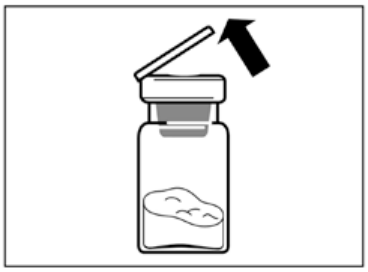
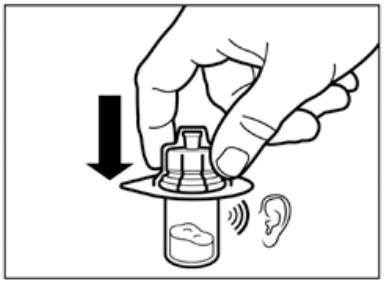
Step 2

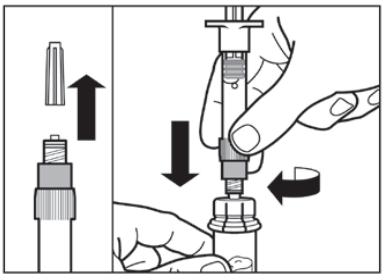
- Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.
- Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.
- Holding the vial adapter packaging, position the vial adapter on top of the vial and push 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.

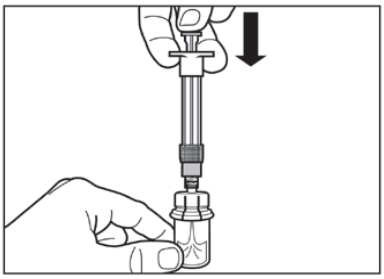




Step 3

- 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.





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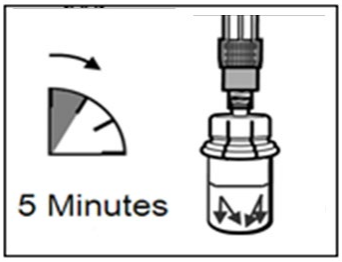
Step 4

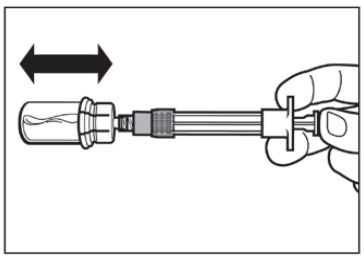
ATTENTION: It is essential to let the vial stand for 5 minutes to ensure that the diluent has fully saturated the powder.



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

- At this stage prepare the patient for injection.

Step 5

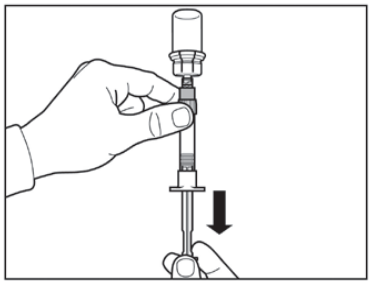


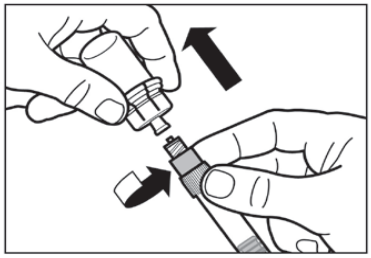
- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.

ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction **for a minimum of 30 seconds** so that the powder is completely suspended (milky uniform suspension). **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**

Step 6

- Prepare injection site with an alcohol wipe.
- Turn syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe.
- Unscrew the syringe from the vial adapter.





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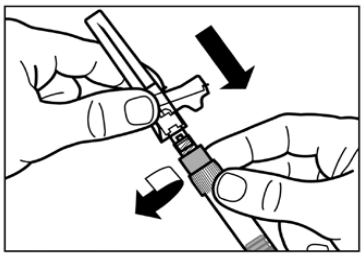
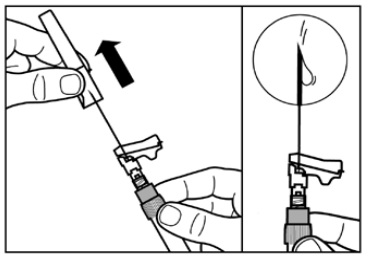
Step 7

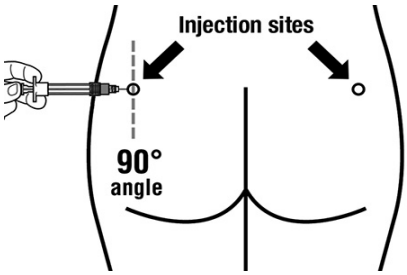


- Screw the safety injection needle onto the syringe.
- If immediate administration is delayed, gently re-shake the syringe to ensure a milky uniform suspension.
- Prepare injection site with an alcohol wipe.
- Pull the protective cover straight off the needle.
- Gently tap the syringe to remove any visible bubbles and expel them from the syringe.



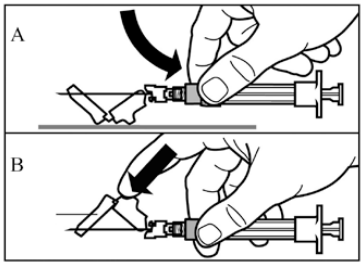
- Proceed **immediately** to Step 8 for administration to the patient. Any delay may result in sedimentation.

Step 8

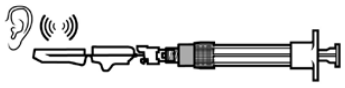


- Sandostatin LAR must be given only by deep intragluteal injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90º angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- Depress the plunger with steady pressure until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in **Step 9**).

Step 9



- 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 the proper activation.
- Dispose of syringe immediately (in a sharps container).

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NOVARTIS

SANDOSTATIN® LAR®

(octreotide acetate)

10 mg*, 20 mg, 30 mg serbuk injeksi dan pelarut untuk suspensi injeksi

Informasi Produk untuk Pasien

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Mohon dibaca leaflet ini dengan hati-hati sebelum menggunakan SANDOSTATIN LAR

Simpan leaflet ini. Anda mungkin akan membutuhkannya untuk dibaca kembali.

Jika Anda memiliki pertanyaan terkait dengan obat ini, mohon tanyakan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

Obat ini diresepkan untuk Anda. Mohon jangan memberikan obat ini kepada orang lain; jangan menggunakan obat ini untuk mengobati penyakit lain.

Jika terjadi efek samping yang berat, atau Anda mengetahui adanya efek samping yang tidak disebutkan dalam leaflet ini, mohon informasikan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

Daftar isi

1 Apakah Sandostatin LAR dan apa kegunaannya

Apakah Sandostatin LAR itu

Sandostatin LAR adalah senyawa sintesis yang berasal dari somatostatin. Somatostatin normalnya ditemukan dalam tubuh manusia, yang berperan menghambat pelepasan hormon tertentu, seperti hormon pertumbuhan. Kelebihan dari Sandostatin LAR dibanding somatostatin adalah lebih kuat dan efeknya bertahan lebih lama.

Apakah kegunaan Sandostatin LAR

Sandostatin LAR merupakan obat yang hanya dapat diresepkan oleh dokter yang digunakan untuk:

Pengobatan akromegali

- yang sudah cukup terkontrol dengan pengobatan Sandostatin s.c.
- pada pasien yang tidak cocok untuk menjalani operasi, radioterapi, atau pengobatan dengan agonis dopamin (atau cara-cara pengobatan ini tidak efektif), atau sebagai

terapi sementara sambil menunggu radioterapi menjadi sepenuhnya efektif (lihat dosis dan cara pemberian)

Meredakan gejala-gejala terkait tumor neuroendokrin gastroenteropankreatik:

- Tumor karsinoid dengan gambaran sindrom karsinoid
- VIPoma
- Glukagonoma

Pengobatan pasien dengan tumor neuroendokrin stadium lanjut pada *midgut*.

2 Apa yang harus Anda ketahui sebelum dan selama menggunakan Sandostatin LAR

Ikuti petunjuk dari dokter Anda secara seksama. Informasi yang Anda dapatkan dari dokter mungkin berbeda dengan informasi umum yang tertera pada brosur ini.

Baca penjelasan berikut sebelum Anda menggunakan Sandostatin LAR.

Jangan menggunakan Sandostatin LAR

- **Jika Anda hipersensitif (alergi)** terhadap octreotide atau kandungan lain dari obat Sandostatin LAR yang tertulis pada bagian 6 – Informasi lebih lanjut pada brosur ini.

Jika ini berlaku untuk Anda, beritahukan dokter Anda tanpa menggunakan Sandostatin LAR.

Jika Anda merasa alergi, mintalah nasihat dokter Anda.

Pemantauan selama pengobatan dengan Sandostatin LAR

- Jika Anda terdiagnosis memiliki batu empedu saat ini, atau pernah mengalaminya, atau mengalami salah satu dari komplikasi berikut: demam, menggigil, sakit perut, atau kulit/mata menguning, beritahukan dokter Anda, mengingat konsumsi Sandostatin LAR berkepanjangan dapat menyebabkan pembentukan batu empedu.
- Dokter akan memeriksa kandung empedu Anda secara berkala.
- Jika Anda memiliki riwayat kekurangan vitamin B12, dokter akan memeriksa kadar B12 Anda secara berkala.
- Jika Anda menjalani pengobatan jangka panjang dengan Sandostatin LAR, dokter akan memeriksa fungsi tiroid Anda secara berkala.
- Mohon beritahukan dokter Anda jika Anda menyandang diabetes karena Sandostatin LAR dapat mempengaruhi kadar gula darah. Jika Anda penyandang diabetes, kadar gula darah Anda harus diperiksa secara rutin.
- Mohon beritahukan dokter Anda jika Anda sedang menggunakan obat-obat lain untuk mengontrol tekanan darah (misalnya *beta-blockers* atau *calcium-channel blockers*) atau obat-obat untuk mengontrol keseimbangan cairan dan elektrolit. Penyesuaian dosis mungkin diperlukan.

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Menggunakan obat-obat lain

Sandostatin LAR dapat mengganggu beberapa obat lain.

Beritahukan dokter atau apoteker Anda, jika Anda sedang atau pernah menggunakan obat-obat lain, termasuk obat-obat yang dapat dibeli tanpa resep dokter.

Pada umumnya, Anda dapat terus melanjutkan konsumsi obat-obat lain sekalipun tengah menjalani pengobatan Sandostatin LAR. Namun, obat-obat tertentu (seperti simetidin, siklosporin, bromokriptin, quinidine dan terfenadin) akan dipengaruhi oleh Sandostatin LAR.

Jika Anda sedang menggunakan obat-obatan untuk mengontrol tekanan darah (seperti *beta blocker* atau *calcium channel blocker*) atau obat untuk mengontrol cairan dan keseimbangan elektrolit, dapat dilakukan penyesuaian dosis oleh dokter Anda.

Jika Anda penyandang diabetes, dokter Anda boleh jadi perlu menyesuaikan pengobatan antidiabetes Anda.

Anak-anak dan remaja (di bawah 18 tahun)

Karena hanya sedikit pengalaman penggunaan obat ini pada anak, Sandostatin LAR tidak diindikasikan untuk pasien anak.

Orang tua (65 tahun ke atas)

Pengalaman dengan Sandostatin LAR telah menunjukkan bahwa tidak ada persyaratan khusus untuk pasien berusia 65 tahun ke atas.

Kehamilan dan menyusui

Mintalah saran dokter atau apoteker Anda sebelum minum obat apa pun.

Beritahukan kepada dokter jika Anda sedang hamil, atau berencana hamil.

- Sandostatin LAR seharusnya hanya digunakan selama kehamilan jika memang benar-benar diperlukan.
- Tidak diketahui apakah Sandostatin LAR dapat menembus masuk ke air susu ibu (ASI). Tidak ada pengalaman penggunaan Sandostatin LAR pada ibu menyusui. Menyusui tidak direkomendasikan selama pengobatan dengan Sandostatin LAR.

Pasien wanita yang berpotensi hamil

Pasien wanita yang berpotensi hamil harus menggunakan metode kontrasepsi yang efektif selama pengobatan dengan Sandostatin LAR.

Mengemudi dan mengoperasikan mesin

Tidak ada informasi tentang efek Sandostatin LAR pada kemampuan Anda untuk mengemudi dan mengoperasikan mesin.

3 Bagaimana cara pemberian Sandostatin LAR

Sandostatin LAR harus selalu diberikan melalui suntikan ke otot bokong. Karena pemberiannya berulang, penyuntikan harus dilakukan secara bergantian pada bokong kiri dan kanan.

Dosis awal biasanya 20 mg Sandostatin LAR, yang diberikan berselang 4 minggu sekali. Setelah sekitar 3 bulan pertama pengobatan dengan Sandostatin LAR, dokter Anda mungkin akan mengkaji ulang pengobatan Anda. Pengkajian ini dapat meliputi pengukuran kadar hormon pertumbuhan atau hormon lain dalam darah Anda. Tergantung hasil yang diperoleh, dan bagaimana kondisi Anda, dosis Sandostatin LAR mungkin perlu diubah. Dosis yang diberikan di setiap suntikan dapat dikurangi menjadi 10 mg* atau, jika pengobatan tidak sepenuhnya efektif, dapat ditingkatkan hingga 30 mg. Jika Anda mendapat Sandostatin LAR untuk mengobati akromegali, dosisnya dapat ditingkatkan lagi menjadi 40 mg, jika perlu. Setelah dosis yang paling sesuai untuk Anda telah ditemukan, dokter Anda mungkin akan mengkaji ulang pengobatan Anda sekitar 6 bulan sekali.

Jika sebelumnya Anda sudah mendapatkan hasil yang baik dengan pengobatan Sandostatin subkutan, Anda dapat segera memulai pengobatan dengan Sandostatin LAR seperti yang dijelaskan di atas. Jika sebelumnya Anda belum pernah diobati dengan Sandostatin subkutan, dapat dimulai dengan pengobatan subkutan dengan periode singkat untuk melihat respons Anda, sebelum beralih ke Sandostatin LAR.

Tergantung pada indikasi khusus yang menjadi alasan Anda diberikan Sandostatin LAR, Anda mungkin perlu terus menggunakan Sandostatin subkutan selama sekitar 2 minggu setelah injeksi Sandostatin LAR pertama. Jika Anda mendapat Sandostatin LAR untuk pengobatan tumor neuroendokrin pada usus, dosis lazim adalah 30 mg berselang 4 minggu sekali. Dokter Anda akan memutuskan berapa lama Anda harus diobati dengan Sandostatin LAR.

Apabila Anda diberikan Sandostatin lebih dari yang seharusnya

Reaksi mengancam-jiwa belum pernah dilaporkan pada kasus overdosis Sandostatin LAR.

Gejala overdosis antara lain muka merah *(hot flushes)*, sering buang air kecil, kelelahan, depresi, kecemasan, dan kurangnya konsentrasi.

Jika Anda menduga terjadi overdosis dan Anda mengalami gejala seperti di atas, segera hubungi dokter Anda.

Apabila Anda lupa menggunakan Sandostatin LAR

Apabila jadwal suntikan Anda terlewat, disarankan agar Anda segera mendapat suntikan Sandostatin LAR begitu teringat, kemudian lanjutkan seperti biasa. Tidak berbahaya jika suntikan terlambat beberapa hari, tetapi Anda bisa saja mengalami kembali beberapa gejala untuk sementara waktu sampai Anda kembali ke jadwal pengobatan yang seharusnya.

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4 Kemungkinan efek samping

Sebagaimana semua obat, Sandostatin LAR dapat menyebabkan beberapa efek samping, meskipun tidak semua orang mengalaminya. Jika Anda mengalaminya, segera beritahukan kepada dokter Anda.

Beberapa efek samping yang berpotensi serius dan membutuhkan pertolongan medis segera

Sangat umum: *(dapat mempengaruhi lebih dari 1 di antara 10 pasien)*

- Batu empedu, menyebabkan nyeri punggung mendadak.
- Kadar gula dalam darah yang berlebih.

Umum: *(dapat mempengaruhi 1-10 di antara 100 pasien)*

- Kelenjar tiroid yang kurang aktif (hipotiroidisme) menyebabkan perubahan pada detak jantung, nafsu makan, atau berat badan; kelelahan, kedinginan, atau bengkak di bagian depan leher.
- Perubahan pada parameter uji fungsi tiroid.
- Radang kandung empedu (kolesistitis); gejala termasuk nyeri di bagian kanan atas perut; demam; mual; kuning pada kulit dan mata.
- Rendahnya kadar gula dalam darah.
- Gangguan toleransi glukosa.
- Detak jantung yang lambat.

Tidak umum: *(terjadi pada kurang dari 1 di antara 100 pasien, tetapi lebih dari 1 di antara 1000 pasien)*

- Haus, volume urin sedikit, urin gelap, kulit kering dan kemerahan *(flushed skin)*.
- Detak jantung cepat.

Efek samping serius lainnya

Jika salah satu dari efek samping berikut ini terjadi pada Anda, beritahukan segera kepada dokter Anda.

- Reaksi hipersensitivitas (alergi), termasuk ruam kulit.
- Salah satu jenis reaksi alergi (anafilaksis) yang menyebabkan sesak napas atau pusing, bengkak dan kesemutan, kemungkinan penurunan tekanan darah dengan pusing atau kehilangan kesadaran.
- Peradangan kelenjar pankreas (pankreatitis).
- Peradangan hati (hepatitis); gejalanya dapat meliputi kulit dan mata kuning (ikterus), mual, muntah, kehilangan nafsu makan, merasa tidak enak badan, gatal, urin berwarna terang.

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- Detak jantung yang tidak teratur.
- Rendahnya jumlah trombosit di dalam darah; ini dapat menghasilkan pendarahan atau memar.

Efek samping lain

Efek samping pada daftar di bawah ini biasanya ringan dan cenderung mereda seiring berjalannya pengobatan.

Sangat umum: *(dapat mempengaruhi lebih dari 1 di antara 10 orang)*

- Diare.
- Nyeri perut.
- Mual.
- Konstipasi (susah buang air besar).
- Perut kembung (masuk angin).
- Sakit kepala.
- Rasa sakit di sekitar tempat pemberian suntikan.

Umum: *(dapat mempengaruhi 1-10 di antara 100 pasien)*

- Rasa tidak nyaman di lambung setelah makan (dispepsia).
- Muntah.
- Begah.
- Feses berlemak.
- Feses encer.
- Perubahan warna feses.
- Pusing.
- Hilangnya nafsu makan.
- Perubahan pada parameter uji fungsi hati.
- Rambut rontok.
- Napas terasa pendek.
- Lemah

Jika Anda mengalami efek samping yang tidak disebutkan dalam brosur ini, mohon beritahukan kepada dokter atau apoteker Anda.

5 Cara penyimpanan Sandostatin LAR

- Jangan menggunakan Sandostatin LAR setelah tanggal kedaluwarsa yang tercantum pada kemasan.

- Simpanlah pada suhu 2° sampai 8°C (di lemari es). Jangan dibekukan. Simpanlah vial pada dus aslinya supaya terhindar dari pajanan cahaya langsung.
- Sandostatin LAR dapat disimpan di bawah suhu 25°C pada hari akan diinjeksikan, tetapi harus disimpan pada dus aslinya agar tidak terpajan cahaya langsung. Suspensi hanya boleh disiapkan segera sebelum injeksi.
- Jauhkan obat dari penglihatan dan jangkauan anak-anak.
- Jangan gunakan obat ini jika Anda melihat partikel atau perubahan warna. Jangan buang obat melalui wastafel atau tempat sampah. Tanyakan pada Apoteker bagaimana cara membuang obat Anda yang sudah lama tidak digunakan. Hal ini akan membantu melindungi lingkungan.

6 Informasi lebih lanjut

Sandostatin LAR adalah depot suntikan jangka panjang.

Zat aktif dari Sandostatin LAR adalah octreotide (setara dengan octreotide acetate) dalam bentuk serbuk (*microspheres*) untuk suspensi injeksi. Serbuk injeksi ini juga mengandung beberapa zat tambahan tidak aktif: poli (DL-laktida-ko-glikolida) dan manitol.

Sebelum obat ini digunakan, serbuk injeksi harus disuspensikan ke dalam cairan khusus (pelarut) yang telah disediakan.

Produk ini mengandung kurang dari 1 mmol (23 mg) natrium per dosisnya, terutama berupa 'natrium bebas'.

7 Informasi untuk tenaga profesional kesehatan

Informasi terkait instruksi untuk injeksi intramuskular Sandostatin LAR, bagaimana bentuk dan apa isi di dalamnya ditujukan kepada dokter Anda, yang akan menyimpan, menangani dan menyuntikan Sandostatin LAR. Untuk informasi lebih lanjut, dapat merujuk pada brosur obat.

Kemasan

Sandostatin LAR dikemas dalam satu set preparat.

Sandostatin LAR 20 mg

Dus, vial 6 mL @ 625 mg + 1 *pre-filled syringe* @ 2 mL berisi pelarut + 1 vial adapter + 1 *safety injection needle*

No. Reg. DKI0567505144B1

Sandostatin LAR 30 mg

Dus, vial 6 mL @ 900 mg + 1 *pre-filled syringe* @ 2 mL berisi pelarut + 1 vial adapter + 1 *safety injection needle*

No. Reg. DKI0567505144C1

HARUS DENGAN RESEP DOKTER

Pemegang Nomor Ijin Edar

PT Novartis Indonesia, Jakarta, Indonesia

Pabrik Pembuat

Sandoz GmbH, Langkampfen, Austria untuk Novartis Pharma AG, Basel, Swiss

**Disclaimer:* Sandostatin LAR 10 mg tidak terdaftar dan tidak dipasarkan di Indonesia

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