NOVARTIS

## Sandostatin® LAR®

Anti-growth hormone

## DESCRIPTION AND COMPOSITION

## Pharmaceutical form

Powder and solvent for suspension for injection

Powder: white to white with yellowish tint powder.

Solvent for suspension for injection: clear, colorless 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.

### Active substance

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.

Certain dosage strengths may not be available in all countries.

### Excipients

### Vial

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

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.

Pharmaceutical formulations may vary between countries.

## INDICATIONS

Treatment of patients with acromegaly:

- *who are adequately controlled on s.c. treatment with Sandostatin®*
- *in whom* surgery or radiotherapy or dopamine agonist treatment is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see DOSAGE AND ADMINISTRATION).

Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumors *in whom symptoms are adequately controlled* on s.c. treatment with Sandostatin:

- Carcinoid tumors with features of the carcinoid syndrome.
- VIPomas.
- Glucagonomas.
- Gastrinomas/Zollinger-Ellison syndrome.
- Insulinomas, for pre-operative control of hypoglycemia and for maintenance therapy.
- GRFomas.

Treatment of patients with advanced Neuroendocrine Tumors of the midgut or unknown primary tumor location where non-midgut sites of origin have been excluded.

## DOSAGE REGIMEN AND ADMINISTRATION

### Dosage regimen

### General target population

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 INSTRUCTIONS FOR USE AND HANDLING).

### Acromegaly

For *patients who are adequately controlled* with s.c. 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 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 2.5 microgram/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF 1 serum concentrations normalized, 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 IGF 1 should be made every 6 months.

## Gastro-entero-pancreatic endocrine tumors

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

For patients in whom symptoms are adequately controlled with s.c. Sandostatin, it is recommended to start treatment with the administration of 20 mg Sandostatin LAR at 4-week intervals. Patients on treatment with s.c. Sandostatin should continue at the previously effective dosage for 2 weeks after the first injection of Sandostatin LAR.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 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.

### Treatment of patients with advanced Neuroendocrine Tumors of the midgut or unknown primary tumor location

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

## Special populations

## Renal impairment

Impaired renal function did not affect the total exposure (AUC) 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.

### Geriatric patients (65 years or above)

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

### Pediatric patients (below 18 years)

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

## CONTRAINDICATIONS

Known hypersensitivity to octreotide or to any of the excipients, (see section DESCRIPTION AND COMPOSITION).

## 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 tumor 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 child-bearing 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.

### 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 however 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 hyperglycemia 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 glycemia. 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 hypoglycemia. 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.

## 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 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 with radioactive somatostatin analogues

Somatostatin and its analogues such as octreotide competitively bind to somatostatin receptors and may interfere with the efficacy of radioactive somatostatin analogues.

The administration of Sandostatin LAR should be avoided for at least 4 weeks prior to the administration of lutetium ($^{177}$Lu) oxodotreotide (Lutathera®), a radiopharmaceutical binding to somatostatin receptors. If necessary, patients may be treated with short acting somatostatin analogues until 24 hours prior to the administration of lutetium ($^{177}$Lu) oxodotreotide.

After administration of lutetium ($^{177}$Lu) oxodotreotide, treatment with Sandostatin LAR can be resumed within 4 to 24 hours and should be discontinued again 4 weeks prior to the next administration of lutetium ($^{177}$Lu) oxodotreotide.

## 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.

### 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).

## 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, decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycemia.

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

#### 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**

| | |
|---|---|
| **Gastrointestinal disorders** | |
| Very common: | Diarrhea, abdominal pain, nausea, constipation, flatulence. |
| Common: | Dyspepsia, vomiting, abdominal distension, steatorrhea, loose stools, faeces discoloured. |
| **Nervous system disorders** | |
| Very common: | **Headache.** |
| Common: | **Dizziness.** |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased Total T4, and decreased Free T4). |
| **Hepatobiliary disorders** | |
| Very Common: | Cholelithiasis. |
| Common: | Cholecystitis, biliary sludge, hyperbilirubinemia. |

| | |
|---|---|
| **Metabolism and nutrition disorders** | |
| Very common: | Hyperglycemia. |
| Common: | Hypoglycemia, glucose tolerance impaired, decrease appetite. |
| Uncommon: | Dehydration. |
| **General disorders and administration site** | |
| Very common: | Injection site reaction pain. |
| Common | Asthenia |
| **Investigations** | |
| Common: | Transaminase increased. |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Pruritus, rash, alopecia |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnea. |
| **Cardiac disorders** | |
| Common: | Bradycardia. |
| Uncommon: | Tachycardia. |

## 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.

**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,** |
| Skin and subcutaneous tissue disorders | **Urticaria.** |
| Hepatobiliary disorders | **Pancreatitis acute, acute hepatitis without cholestasis, hepatitis cholestatic, cholestasis, jaundice, jaundice cholestatic.** |
| Cardiac disorders | **Arrhythmias.** |
| 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. (See 'Recommendation for the management of patients during Sandostatin LAR treatment with respect to the development of gallstones' at the end of this document).

**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 FOR USE).

**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.

**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.

## 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.

## CLINICAL PHARMACOLOGY

### 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 glucagon,
- 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 normalizing 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, paresthesia, fatigue, osteoarthralgia and carpal tunnel syndrome. In previously untreated acromegaly patients with GH-secreting pituitary adenoma, Sandostatin LAR treatment resulted in a median reduction in tumor volume of 20.6% in one study (49 patients) at 24 weeks and 24.5% in another study (94 patients) at 24 weeks and 36.2% at 48 weeks.

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 diarrhea. 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 diarrhea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. In some patients, computerized tomography scanning suggests a slowing or arrest of progression of the tumor, 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 octreotide 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 diarrhea, and hence weight gain, in those patients affected. Although administration of octreotide 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.

**Gastrinomas/Zollinger-Ellison syndrome**:

Although therapy with proton pump inhibitors or $H_2$-receptor blocking agents controls the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid, such control may be incomplete. Diarrhea may also be a prominent symptom not alleviated in all patients by this therapy. Octreotide alone or in conjunction with proton pump inhibitors or $H_2$-receptor antagonists may reduce gastric acid hypersecretion and improve symptoms, including diarrhoea. Other symptoms possibly due to peptide production by the tumor, e.g. flushing, may also be relieved. Plasma gastrin levels fall in some patients.

**Insulinomas**:

Administration of octreotide produces a fall in circulating immunoreactive insulin. In patients with operable tumours, octreotide may help to restore and maintain normoglycaemia pre-operatively. In patients with inoperative benign or malignant tumors, glycaemic control may be improved even without concomitant sustained reduction in circulating insulin levels.

**GRFomas**:

These rare tumors are characterized by production of GH releasing factor (GRF) alone or in conjunction with other active peptides. Octreotide produces improvement in the features and symptoms of the resulting acromegaly. This is probably due to inhibition of GRF and GH secretion, and a reduction in pituitary enlargement may follow.

## 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 a low undetectable octreotide level within 24 hours. After this initial 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 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 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 patients with acromegaly, plateau octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg Sandostatin LAR amount to 358 ng/L, 926 ng/L, and 1,710 ng/L, respectively. Steady-state octreotide serum 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 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 and 30 mg of Sandostatin LAR given at 4 week intervals also increased linearly with dose and were 1,231 (894) ng/L, 2,620 (2,270) ng/L and 3,928 (3,010) 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.

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 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.

## CLINICAL STUDIES

### Advanced Neuroendocrine Tumors of the midgut or unknown primary tumor location

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.

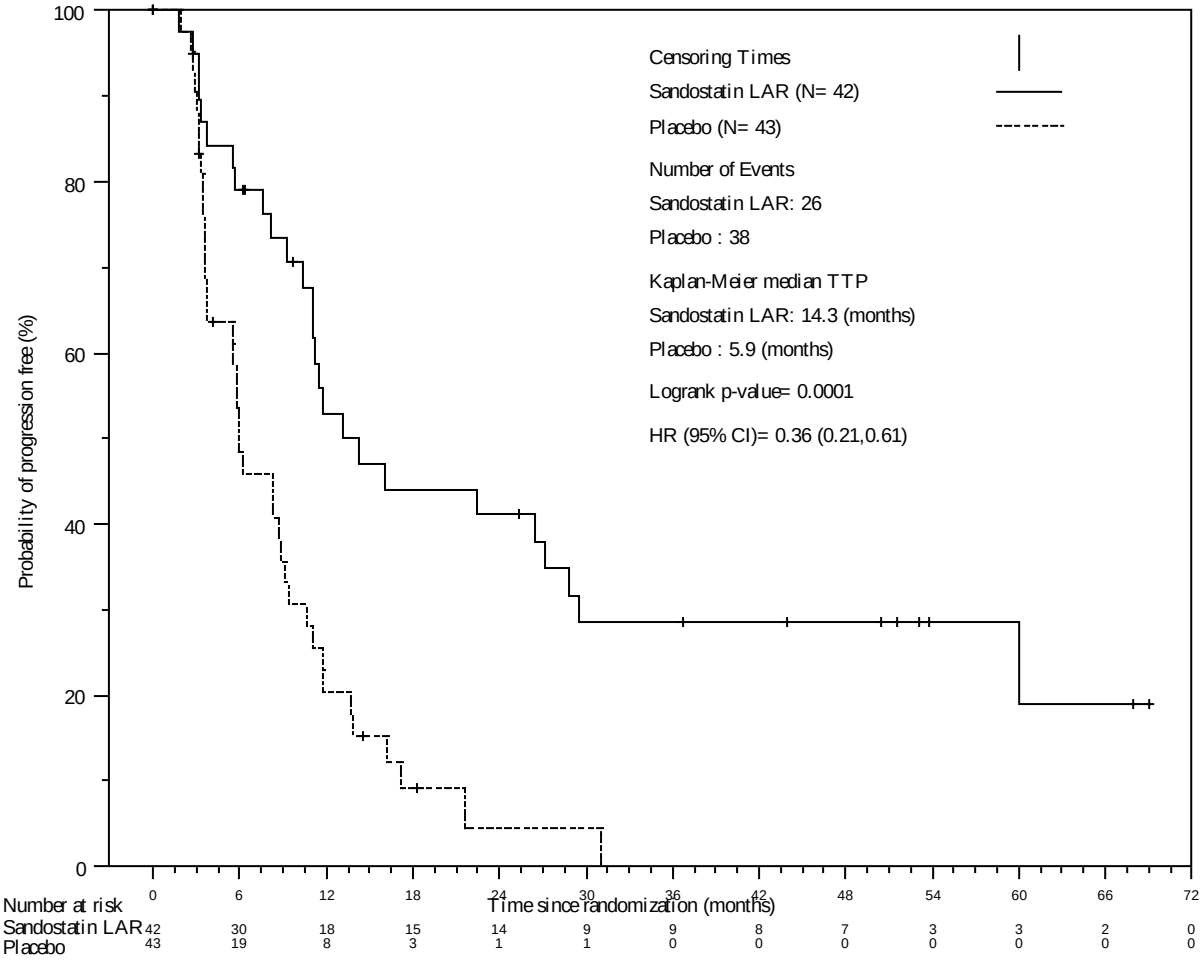
Main inclusion criteria were: treatment naïve; histologically confirmed; locally inoperable or metastatic well-differentiated; functionally active or inactive neuroendocrine tumors/carcinomas; with primary tumor located in the midgut or unknown origin believed to be of midgut origin if a primary within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

Sandostatin LAR was superior to placebo for TTP with 26 and 38 progressions or tumor-related deaths in the Sandostatin LAR and placebo groups, respectively (HR = 0.36; 95% CI,0.21 to 0.61; p-value =.0001). (see Fig 1)

Median time to tumor progression was 14.3 months (95% CI, 11.0 to 28.8 months) in the Sandostatin LAR group and 5.9 months (95% CI, 3.7 to 9.2 months) in the placebo group.

**Figure 1 Kaplan-Meier plot for time to progression by treatment group (Full analysis set)**




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 functioning (HR = 0.41; 95% CI, 0.18 to 0.92) and non-functioning tumors (HR = 0.32; 95% CI, 0.15 to 0.66).

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

After an additional 4.5 years of follow-up, the hazard ratio of Sandostatin LAR versus placebo for overall survival was 0.86 (95% CI: 0.46, 1.60) favoring Sandostatin LAR. The overall survival results should be interpreted with caution due to the low number of events and the large number of patients in the placebo group who received follow-up therapy with somatostatin analogues

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

## NON-CLINICAL SAFETY DATA

### Repeat dose toxicity

In two repeat 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

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. *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. injection site after 52, 104 and 113/116 weeks. Local tumours occurred also in the control rats, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced 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 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.

### Reproduction 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 ratswhich 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.

## PHARMACEUTICAL INFORMATION

## INCOMPATIBILITIES

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

## STORAGE

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Keep vial in the outer carton in order to protect it from light. Sandostatin LAR can remain below 25°C on the day of injection. However, the suspension must only be prepared immediately prior to i.m. injection.

Sandostatin LAR should not be used after the date marked “EXP” on the pack.

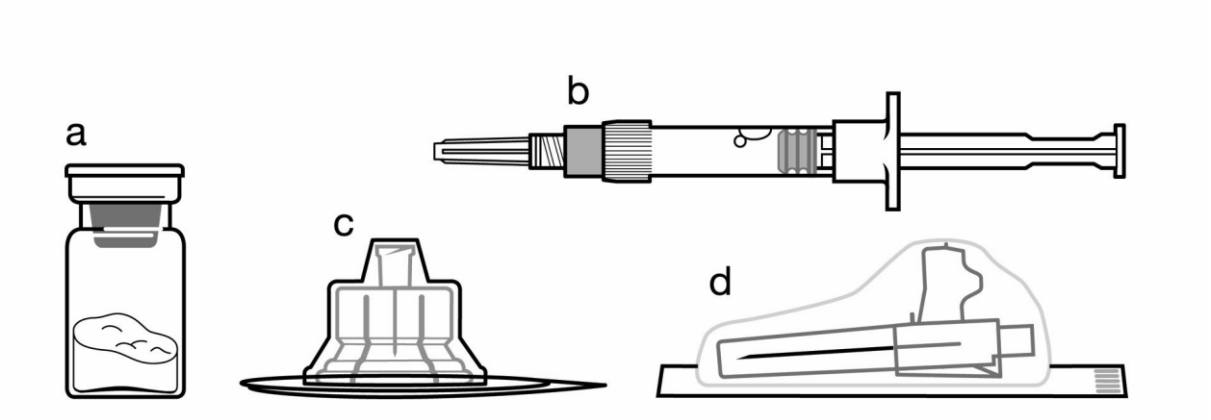
## INSTRUCTIONS FOR USE AND HANDLING

### Kit with vial adapter and safety needle

## Instructions for preparation and 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 proper reconstitution of Sandostatin LAR before deep intragluteal 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.

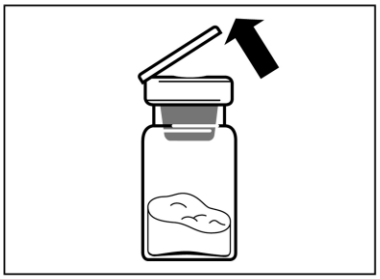
## Step 1

- Remove the Sandostatin LAR injection kit from refrigerated storage

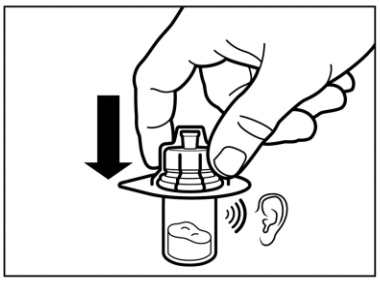

**ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature**. **Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution,** but do not exceed 24 hours.

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

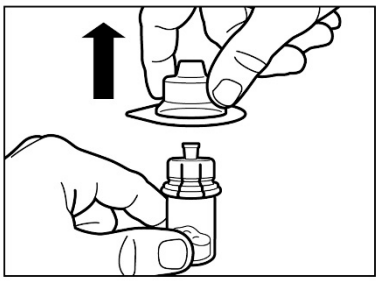
## Step 2



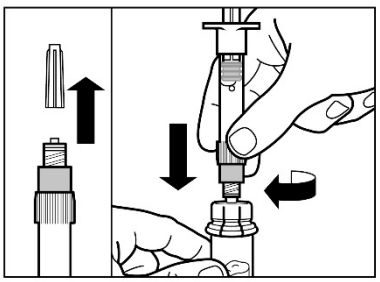
- Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.
- Remove the lid film of the vial adapter packaging but Do NOT remove the vial adapter from its packaging.
- Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible "click".



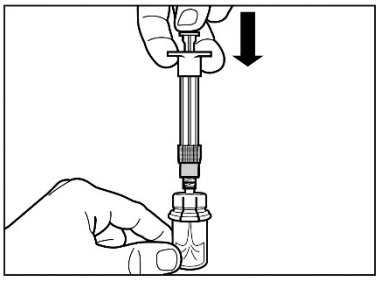
- Lift the packaging off the vial adapter with a vertical movement.



## Step 3

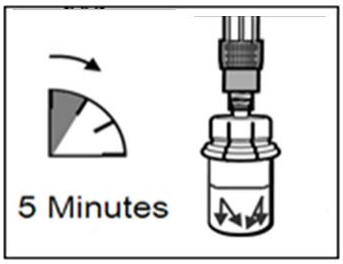


- Remove the cap from the syringe prefilled with the diluent solution and screw the syringe onto the vial adapter.
- Slowly push the plunger all the way down to transfer all the diluent solution in the vial.



### Step 4

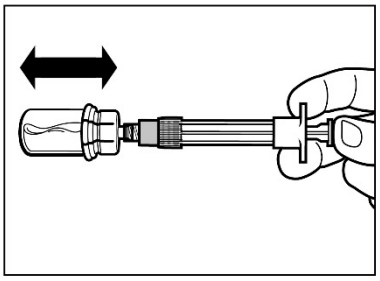
**ATTENTION: It is essential to let the vial stand for 5 minutes** to ensure that the diluent has fully saturated the powder.




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.

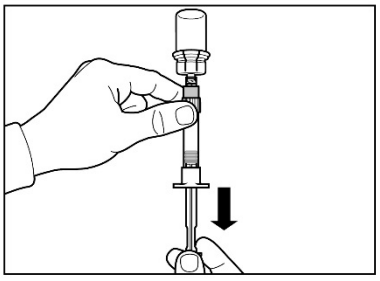
### Step 5



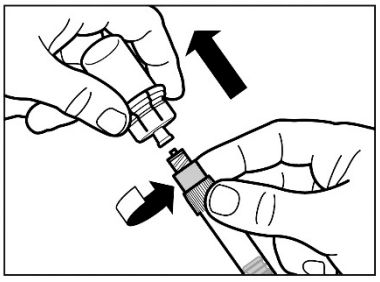
- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.

**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

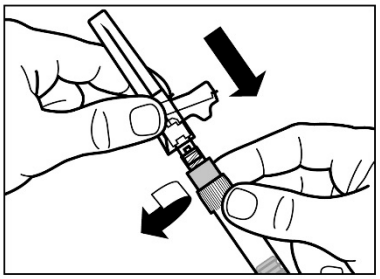


- Prepare injection site with an alcohol wipe
- Turn syringe and vial upside down, **slowly** pull the plunger back and draw the entire contents from the vial into the syringe.

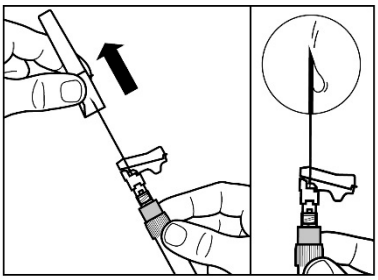


- Unscrew the syringe from the vial adapter.

## Step 7

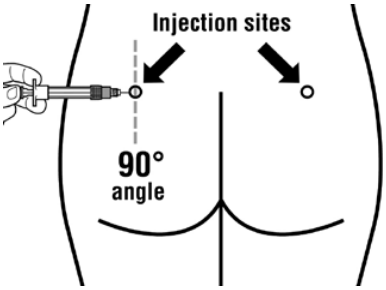


- Screw the safety injection needle onto the syringe.
- Gently re-shake the syringe to ensure a milky uniform suspension



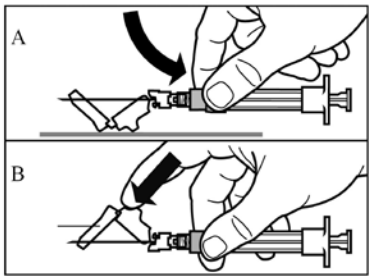
- Pull the protective cover straight off the needle.
- Gently tap the syringe to remove any visible bubbles and expel them from the syringe. Verify that injection site has not been contaminated
- Proceed **immediately** to Step 8 for administration to the patient. Any delay may result in sedimentation

## Step 8

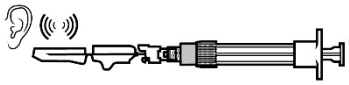



- Sandostatin LAR must be given only by deep intragluteal injection, **Never** intravenously.
- Insert the needle fully into the left or right gluteus at a 90º angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- 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 the syringe immediately in a sharps container.



**Recommendation for the management of patients during Sandostatin LAR treatment with respect to the development of gallstones**

1. Patients should undergo a baseline ultrasound examination of the gallbladder prior to commencing octreotide treatment.
2. Periodic repeat ultrasound examination of the gallbladder should be performed, preferably at about 6-month intervals, throughout Sandostatin LAR treatment.
3. If stones are already present before the start of therapy, the potential benefit of Sandostatin LAR should be assessed against the potential risks associated with the gallstones. There is no evidence at present that Sandostatin LAR adversely affects the course or prognosis of pre-existing gallstones.
4. Management of patients who develop gallstones in association with Sandostatin LAR:
   i. **Asymptomatic gallstones** Sandostatin LAR may be continued, depending on re-assessment of the benefit/risk ratio. Either way, no action is required except to continue monitoring, with increased frequency if this is considered necessary.
   ii. **Symptomatic gallstones**

   Sandostatin LAR may be either stopped or continued, depending on re-assessment of the benefit/risk ratio. Either way, the gallstones should be treated like any other symptomatic gallstones. Medically, this may include combined bile acid therapy (e.g. chenodeoxycholic acid together with ursodeoxycholic acid [UDCA] or monotherapy with ursodeoxycholic acid (UDCA) associated with ultrasound monitoring until the stones have completely disappeared. For posology and treatment duration, please consult the locally approved prescribing information for CDCA and/or UDCA.

## Special precautions for disposal

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

***Note***: Sandostatin LAR must be kept out of the reach and sight of children.

## Manufacturer:

See folding box.

## International Package Leaflet

Information issued: April 2020.SIN

® = registered trademark

## Novartis Pharma AG, Basel, Switzerland