

## **Annex III**

### **Summary of product characteristics, labelling and package leaflet**

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

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

[To be completed nationally]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 10 mg octreotide (as octreotide acetate)  
One vial contains 20 mg octreotide (as octreotide acetate)  
One vial contains 30 mg octreotide (as octreotide acetate)

### Excipients with known effect

Contains less than 1 mmol (23 mg) sodium per dose, i.e is essentially “sodium-free”.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection

Powder: White to white with yellowish tint.

Solvent: Clear, colourless to slightly yellow or brown solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of patients with acromegaly in whom surgery is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see section 4.2).

Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumours e.g. carcinoid tumours with features of the carcinoid syndrome (see section 5.1).

Treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded.

Treatment of TSH-secreting pituitary adenomas:

- when secretion has not normalised after surgery and/or radiotherapy;
- in patients in whom surgery is inappropriate;
- in irradiated patients, until radiotherapy is effective.

### 4.2 Posology and method of administration

#### Posology

#### Acromegaly

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. If after 3 months, GH, IGF-1, and/or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF-1 serum concentrations normalised, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg Sandostatin LAR may be administered every 4 weeks. However, particularly in this group of patients, it is recommended to closely monitor adequate control of serum GH and IGF-1 concentrations, and clinical signs/symptoms at this low dose of Sandostatin LAR.

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

### Gastro-entero-pancreatic endocrine tumours

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

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

*Treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded*

The recommended dose of Sandostatin LAR is 30 mg administered every 4 weeks (see section 5.1). Treatment with Sandostatin LAR for tumour control should be continued in the absence of tumour progression.

### Treatment of TSH-secreting adenomas

Treatment with Sandostatin LAR should be started at a dose of 20 mg at 4-weekly intervals for 3 months before considering dose adjustment. The dose is then adjusted on the basis of the TSH and thyroid hormone response.

### Use in patients with impaired renal function

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.

### Use in patients with impaired hepatic function

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. In certain cases patients with impaired hepatic function may require dose adjustment.

#### Use in the elderly

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

#### Use in children

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

#### Method of administration

Sandostatin LAR may only be administered by deep intramuscular injection. The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle (see section 6.6).

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

#### General

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

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

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

Hepatic function should be monitored during octreotide therapy.

#### Cardiovascular related events

Common cases of bradycardia have been reported. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary (see section 4.5).

#### Gallbladder and related events

Octreotide inhibits secretion of cholecystokinin, resulting in reduced contractility of the gallbladder and an increased risk of sludge and stone formation. 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 tumours suggests that treatment with Sandostatin LAR does not increase the incidence of gallstone formation, compared with s.c. treatment. Ultrasonic examination of the gallbladder before and at about 6-monthly intervals during Sandostatin LAR therapy is however recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

#### 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, the state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

In patients with concomitant Type I diabetes mellitus, Sandostatin LAR is likely to affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and type II diabetics with partially intact insulin reserves, Sandostatin 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 B12 levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B12 levels is recommended during therapy with Sandostatin LAR in patients who have a history of vitamin B12 deprivation.

### Sodium content

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may be necessary when Sandostatin LAR is administered concomitantly (see section 4.4).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin LAR is administered concomitantly (see section 4.4).

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 analogues might decrease the metabolic clearance 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 octreotide may have this effect, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcomes are unknown. The majority of reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during

the first trimester of pregnancy at doses ranging from 100-1200 micrograms/day of Sandostatin s.c. or 10-40 mg/month of Sandostatin LAR. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. No causal relationship to octreotide is suspected for these cases.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Sandostatin LAR during pregnancy (see section 4.4).

### Breastfeeding

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

### Fertility

It is not known whether octreotide has an effect on human fertility. Late descent of the testes was found for male offsprings of dams treated during pregnancy and lactation. Octreotide, however, did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Sandostatin LAR has no or negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with Sandostatin LAR.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most frequent adverse reactions reported during 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 diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness, localised pain, biliary sludge, thyroid dysfunction (e.g., decreased thyroid stimulating hormone [TSH], decreased total T4, and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycaemia.

### Tabulated list of adverse reactions

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

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

**Table 1 Adverse drug reactions reported in clinical studies**

#### **Gastrointestinal disorders**

Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence.
Common:	Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces.

<b>Nervous system disorders</b>	
Very common:	Headache.
Common:	Dizziness.
<b>Endocrine disorders</b>	
Common:	Hypothyroidism, thyroid dysfunction (e.g., decreased TSH, decreased total T4, and decreased free T4).
<b>Hepatobiliary disorders</b>	
Very common:	Cholelithiasis.
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia.
<b>Metabolism and nutrition disorders</b>	
Very common:	Hyperglycaemia.
Common:	Hypoglycaemia, impaired glucose tolerance, anorexia.
Uncommon:	Dehydration.
<b>General disorders and administration site conditions</b>	
Very common:	Injection site reactions.
Common:	Asthenia.
<b>Investigations</b>	
Common:	Elevated transaminase levels.
<b>Skin and subcutaneous tissue disorders</b>	
Common:	Pruritus, rash, alopecia.
<b>Respiratory disorders</b>	
Common:	Dyspnoea.
<b>Cardiac disorders</b>	
Common:	Bradycardia.
Uncommon:	Tachycardia.

#### Post-marketing

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

**Table 2 Adverse drug reactions derived from spontaneous reports**

<b>Immune system disorders</b>
Anaphylaxis, allergy/hypersensitivity reactions.
<b>Skin and subcutaneous tissue disorders</b>
Urticaria
<b>Hepatobiliary disorders</b>
Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.
<b>Cardiac disorders</b>
Arrhythmias.
<b>Investigations</b>
Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels.

#### Description of selected adverse reactions

##### *Gastrointestinal disorders*

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

The frequency of gastrointestinal adverse events is known to decrease over time with continued treatment.

##### *Injection site reactions*

Injection site related reactions including pain, burning, redness, haematoma, haemorrhage, pruritus or swelling were commonly reported in patients receiving Sandostatin LAR; however, these events did not require any clinical intervention in the majority of the cases.

#### *Metabolism and nutrition disorders*

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

#### *Pancreatic enzymes*

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. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term Sandostatin s.c. treatment.

#### *Cardiac disorders*

In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarisation, 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 4.4).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions [via the national reporting system listed in Appendix V.](#)

## **4.9 Overdose**

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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02

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 GEP endocrine system.

In animals, octreotide is a more potent inhibitor of GH, glucagon and insulin release than somatostatin is, 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 endocrine system, and arginine-stimulated release of insulin and glucagon,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH).

Unlike somatostatin, octreotide inhibits GH secretion 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 galenic 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, osteoarthralgia and carpal tunnel syndrome. In previously untreated acromegaly patients with GH-secreting pituitary adenoma, Sandostatin LAR treatment resulted in a tumour volume reduction of >20% in a significant proportion (50%) of patients.

In individual patients with GH-secreting pituitary adenoma, Sandostatin LAR was reported to lead to shrinkage of the tumour (prior to surgery). However, surgery should not be delayed.

For patients with functional tumours 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 tumours are as follows:

#### Carcinoid tumours

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 tumours 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, computed 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 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 diarrhoea, 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

Therapy with proton pump inhibitors or H<sub>2</sub> receptor blocking agents generally controls gastric acid hypersecretion. However, diarrhoea, which is also a prominent symptom, may not be adequately alleviated by proton pump inhibitors or H<sub>2</sub> receptor blocking agents. Sandostatin LAR can help to further reduce gastric acid hypersecretion and improve symptoms, including diarrhoea, as it provides suppression of elevated gastrin levels, 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 normoglycemia pre-operatively. In patients with inoperable benign or malignant tumours, glycaemic control may be improved even without concomitant sustained reduction in circulating insulin levels.

### Advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded

A Phase III, randomised, double-blind, placebo-controlled study (PROMID) demonstrated that Sandostatin LAR inhibits tumour growth in patients with advanced neuroendocrine tumours of the midgut.

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

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

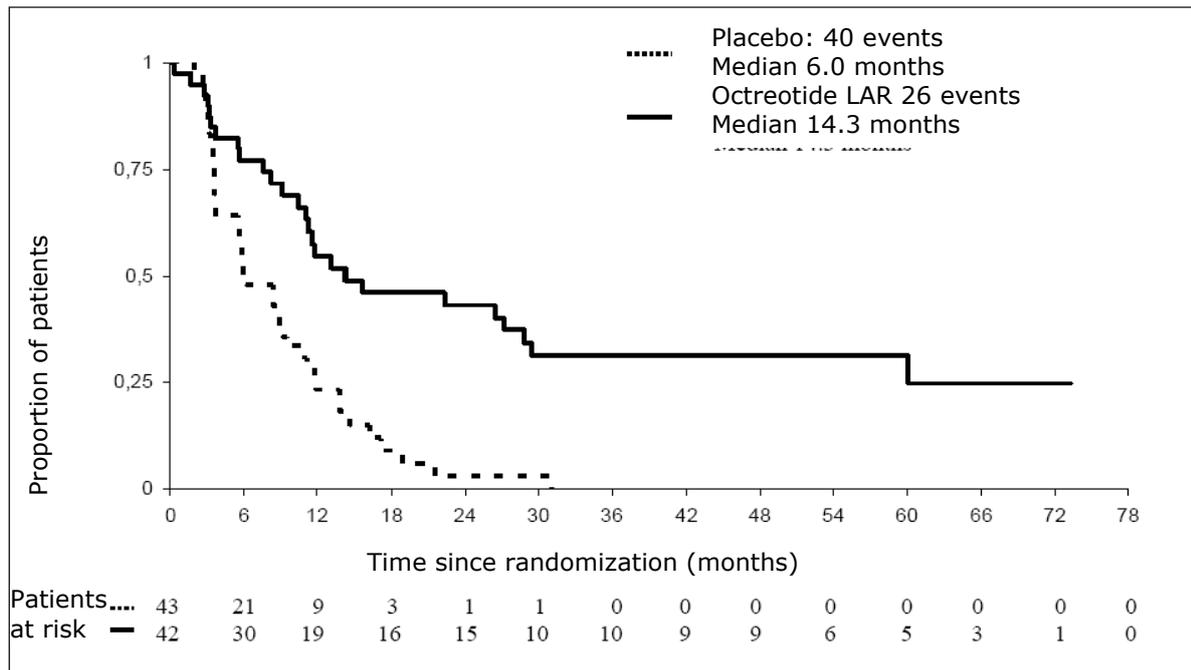
The primary endpoint was time to tumour progression or tumour-related death (TTP).

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 =.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 =.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.

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 =.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 3 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

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

After 6 months of treatment, stable disease was observed in 66% 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.

### Treatment of TSH-secreting pituitary adenomas

Sandostatin LAR, one i.m. injection every 4 weeks, has been shown to suppress elevated thyroid hormones, to normalise TSH and to improve the clinical signs and symptoms of hyperthyroidism in patients with TSH-secreting adenomas. Treatment effect of Sandostatin LAR reached statistical significance as compared to baseline after 28 days and treatment benefit continued for up to 6 months.

## **5.2 Pharmacokinetic properties**

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 tumours, 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.

Pharmacokinetic data with limited blood sampling in pediatric patients with hypothalamic obesity, aged 7–17 years, receiving Sandostatin LAR 40 mg once monthly, showed mean octreotide trough plasma concentrations of 1,395 ng/L after the first injection and of 2,973 ng/L at steady state. A high inter-subject variability is observed.

Steady-state trough octreotide concentrations were not correlated with age and BMI, but moderately correlated with body weight (52.3–133 kg) and was significantly different between male and female patients, i.e. about 17% higher for female patients.

## **5.3 Preclinical safety data**

Acute and repeated dose toxicology, genotoxicity, carcinogenicity and reproductive toxicology studies in animals revealed no specific safety concerns for humans.

Reproduction studies in animals revealed no evidence of teratogenic, embryo/foetal or other reproduction effects due to octreotide at parental doses of up to 1 mg/kg/day. Some retardation of the physiological growth was noted in the offspring of rats which was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity (see section 4.6).

No specific studies were conducted in juvenile rats. In the pre- and post-natal developmental studies, reduced growth and maturation was observed in the F1 offspring of dams given octreotide during the entire pregnancy and lactation period. Delayed descent of the testes was observed for male F1 offsprings, but fertility of the affected F1 male pups remained normal. Thus, the above mentioned observations were transient and considered to be the consequence of GH inhibition.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Powder (Vial):  
Poly(DL-lactide-co-glycolide)  
Mannitol (E421)

Solvent (Prefilled syringe):  
Carmellose sodium  
Mannitol (E421)  
Poloxamer 188  
Water for injections

### **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

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

### **6.4 Special precautions for storage**

Store in the original package in order to protect from light.  
Store in a refrigerator (2°C to 8°C). Do not freeze.  
Sandostatin LAR may be stored below 25°C on the day of the injection.  
For storage conditions after reconstitution, refer to section 6.3.

### **6.5 Nature and contents of container**

Unit packs containing one 6 mL glass vial with rubber stopper (bromobutyl rubber), sealed with an aluminium flip-off seal, containing powder for suspension for injection and one 3 mL colourless pre-filled glass syringe with front and plunger stopper (chlorobutyl rubber) with 2 mL solvent, co-packaged in a sealed blister tray with one vial adapter and one safety injection needle.

Multipacks of three unit packs, each unit pack containing: one 6 mL glass vial with rubber stopper (bromobutyl rubber), sealed with an aluminium flip-off seal, containing powder for suspension for injection and one 3 mL colourless pre-filled glass syringe with front and plunger stopper (chlorobutyl rubber) with 2 mL solvent, co-packaged in a sealed blister tray with one vial adapter and one safety injection needle.

Not all pack sizes may be marketed

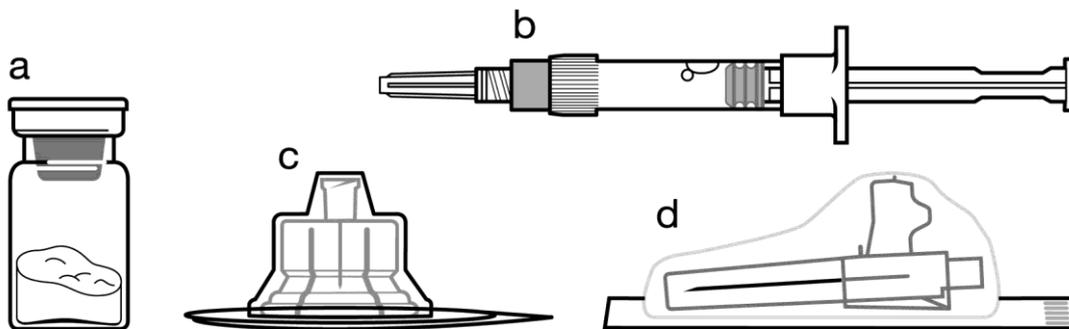
## 6.6 Special precautions for disposal and other handling

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

### Instructions for preparation and intramuscular injection for Sandostatin LAR

FOR DEEP INTRAMUSCULAR INJECTION ONLY

Included in the injection kit:



- 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 intramuscular 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.

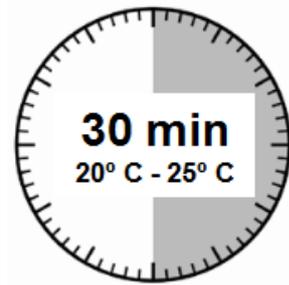
Sandostatin LAR should only be administered by a trained healthcare professional.

### 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.



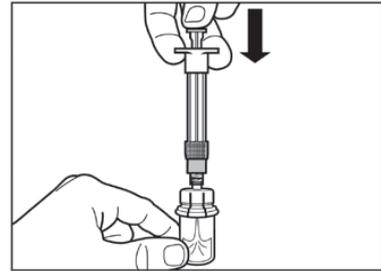
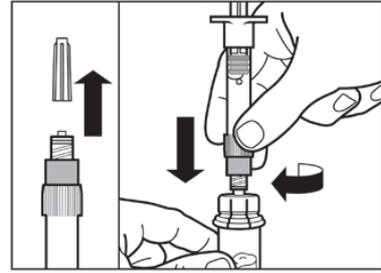
### Step 2

- 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 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.

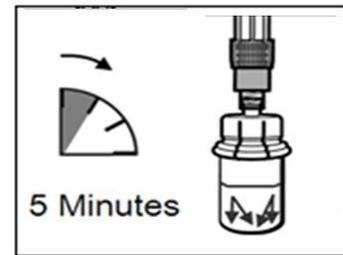


### Step 4

**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.

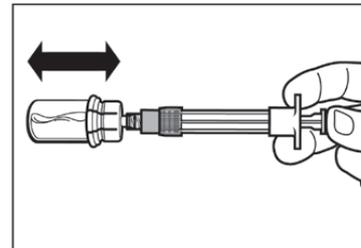
- At this stage prepare the patient for injection.



### Step 5

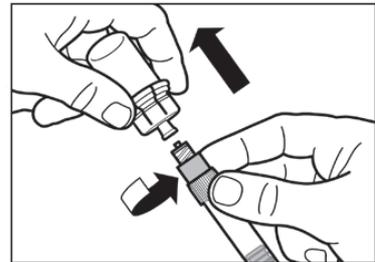
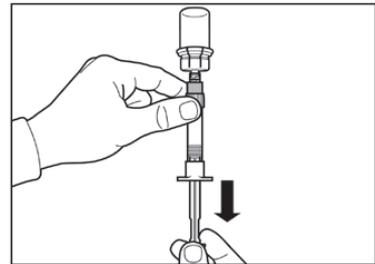
- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.

**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.**



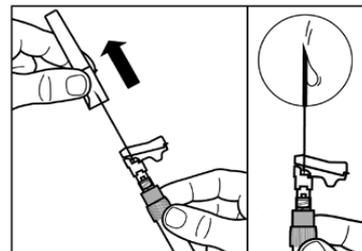
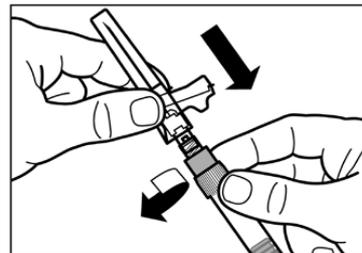
### Step 6

- 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.



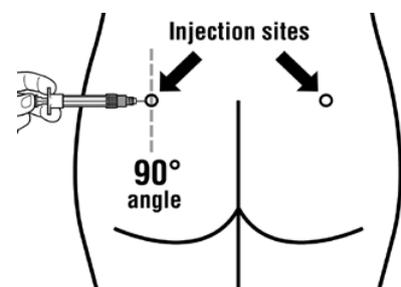
### Step 7

- Screw the safety injection needle onto the syringe.
- 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.



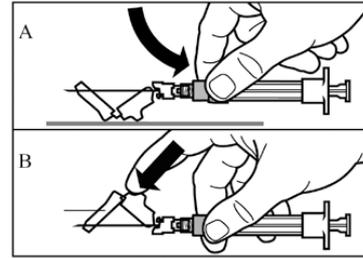
### Step 8

- Sandostatin LAR must be given only by deep intramuscular injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90° angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- 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 two 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).



## 7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

## **LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{OUTER PACKAGING/UNIT PACK}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 10 mg powder and solvent for suspension for injection

[To be completed nationally]

octreotide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 10 mg octreotide (as octreotide acetate)

**3. LIST OF EXCIPIENTS**

Also contains in powder (vial): poly(DL-lactide-co-glycolide), mannitol (E421).

Also contains in solvent (prefilled syringe): carmellose sodium, mannitol (E421), poloxamer 188, water for injections.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

One vial of powder

One pre-filled syringe with 2 ml solvent

One safety injection needle

One vial adapter

[Pack sizes - To be completed nationally]

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Intramuscular use

Single use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store at 2°C to 8°C. Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

[To be completed nationally]

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{OUTER PACKAGING/UNIT PACK}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 20 mg powder and solvent for suspension for injection

[To be completed nationally]

octreotide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 20 mg octreotide (as octreotide acetate)

**3. LIST OF EXCIPIENTS**

Also contains in powder (vial): poly(DL-lactide-co-glycolide), mannitol (E421).

Also contains in solvent (prefilled syringe): carmellose sodium, mannitol (E421), poloxamer 188, water for injections.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

One vial of powder

One pre-filled syringe with 2 ml solvent

One safety injection needle

One vial adapter

[Pack sizes - To be completed nationally]

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Intramuscular use

Single use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store at 2°C to 8°C. Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

[To be completed nationally]

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{OUTER PACKAGING/UNIT PACK}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 30 mg powder and solvent for suspension for injection

[To be completed nationally]

octreotide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 30 mg octreotide (as octreotide acetate)

**3. LIST OF EXCIPIENTS**

Also contains in powder (vial): poly(DL-lactide-co-glycolide), mannitol (E421).

Also contains in solvent (prefilled syringe): carmellose sodium, mannitol (E421), poloxamer 188, water for injections.

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

One vial of powder

One pre-filled syringe with 2 ml solvent

One safety injection needle

One vial adapter

[Pack sizes - To be completed nationally]

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Intramuscular use

Single use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store at 2°C to 8°C. Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

[To be completed nationally]

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{STICKER ON TRANSPARENT FOIL (FOR A MULTIPACK)}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 10 mg powder and solvent for suspension for injection  
octreotide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**8. EXPIRY DATE**

EXP

**13. BATCH NUMBER**

Lot

**14. OTHER INFORMATION**

3 unit packs.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{STICKER ON TRANSPARENT FOIL (FOR A MULTIPACK)}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 20 mg powder and solvent for suspension for injection  
octreotide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**8. EXPIRY DATE**

EXP

**13. BATCH NUMBER**

Lot

**14. OTHER INFORMATION**

3 unit packs.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**{STICKER ON TRANSPARENT FOIL (FOR A MULTIPACK)}**

**1. NAME OF THE MEDICINAL PRODUCT**

SANDOSTATIN LAR 30 mg powder and solvent for suspension for injection

octreotide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**8. EXPIRY DATE**

EXP

**13. BATCH NUMBER**

Lot

**14. OTHER INFORMATION**

3 unit packs.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{VIAL LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 10 mg powder for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

10 mg octreotide

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{VIAL LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 20 mg powder for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

20 mg octreotide

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{VIAL LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 30 mg powder for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

30 mg octreotide

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{PRE-FILLED SYRINGE LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for SANDOSTATIN LAR  
[To be completed nationally]

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

2 ml

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{LIDDING FOIL TRAY LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 10 mg powder and solvent for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

One vial with powder  
One pre-filled syringe with 2 ml solvent  
One safety injection needle  
One vial adapter

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{LIDDING FOIL TRAY LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 20 mg powder and solvent for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

One vial with powder  
One pre-filled syringe with 2 ml solvent  
One safety injection needle  
One vial adapter

**6. OTHER**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**{LIDDING FOIL TRAY LABEL}**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

SANDOSTATIN LAR 30 mg powder and solvent for suspension for injection  
[To be completed nationally]

octreotide  
IM

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

One vial with powder  
One pre-filled syringe with 2 ml solvent  
One safety injection needle  
One vial adapter

**6. OTHER**

[To be completed nationally]

**PACKAGE LEAFLET**

## Package leaflet: Information for the patient

**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**  
[To be completed nationally]

octreotide

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

1. What Sandostatin LAR is and what it is used for
2. What you need to know before you use Sandostatin LAR
3. How to use Sandostatin LAR
4. Possible side effects
5. How to store Sandostatin LAR
6. Contents of the pack and other information

### 1. What Sandostatin LAR is and what it is used for

Sandostatin LAR is a synthetic compound derived from somatostatin. Somatostatin is normally found in the human body, where it inhibits the release of certain hormones such as growth hormone. The advantages of Sandostatin LAR over somatostatin are that it is stronger and its effects last longer.

#### Sandostatin LAR is used

- to treat acromegaly,  
Acromegaly is a condition where the body produces too much growth hormone. Normally, growth hormone controls growth of tissues, organs, and bones. Too much growth hormone leads to an increase in the size of bones and tissues, especially in the hands and feet. Sandostatin LAR markedly reduces the symptoms of acromegaly, which include headache, excessive perspiration, numbness of the hands and feet, tiredness, and joint pain. In most cases, the overproduction of growth hormone is caused by an enlargement in the pituitary gland (a pituitary adenoma); Sandostatin LAR treatment may reduce the size of the adenoma.

Sandostatin LAR is used to treat people with acromegaly:

- when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or haven't worked;
- after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective.
- to relieve symptoms associated with overproduction of some specific hormones and other related substances by the stomach, bowels or pancreas,

Overproduction of specific hormones and other related natural substances can be caused by some rare conditions of the stomach, bowels or pancreas. This upsets the natural hormonal balance of the body and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash, and weight loss. Treatment with Sandostatin LAR helps to control these symptoms.

- to treat neuroendocrine tumours located in the gut (e.g. appendix, small intestine or colon)  
Neuroendocrine tumours are rare tumours which can be found in different parts of the body. Sandostatin LAR is also used to control the growth of these tumours, when they are located in the gut (e.g. appendix, small intestine or colon).

- to treat pituitary tumours that produce too much thyroid-stimulating hormone (TSH).  
Too much thyroid-stimulating hormone (TSH) leads to hyperthyroidism. Sandostatin LAR is used to treat people with pituitary tumours that produce too much thyroid-stimulating hormone (TSH):
  - when other types of treatment (surgery or radiotherapy) are not suitable or have not worked;
  - after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective.

## **2. What you need to know before you use Sandostatin LAR**

Follow all instructions given to you by your doctor carefully. They may differ from the information contained in this leaflet.

Read the following explanations before you use Sandostatin LAR.

### **Do not use Sandostatin LAR:**

- if you are allergic to octreotide or any of the other ingredients of this medicine (listed in section 6).

### **Warnings and precautions**

Talk to your doctor before using Sandostatin LAR:

- if you know that you have gallstones now, or have had them in the past; tell your doctor, as prolonged use of Sandostatin LAR may result in gallstone formation. Your doctor may wish to check your gallbladder periodically.
- if you know that you have diabetes, as Sandostatin LAR can affect blood sugar levels. If you are diabetic, your sugar levels should be checked regularly.
- if you have a history of vitamin B12 deprivation your doctor may wish to check your vitamin B12 level periodically.

### **Test and checks**

If you receive treatment with Sandostatin LAR over a long period of time, your doctor may wish to check your thyroid function periodically.

Your doctor will check your liver function.

### **Children**

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

### **Other medicines and Sandostatin LAR**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You can generally continue taking other medicines while on Sandostatin LAR. However, certain medicines, such as cimetidine, ciclosporin, bromocriptine, quinidine and terfenadine have been reported to be affected by Sandostatin LAR.

If you are taking a medicine to control your blood pressure (e.g. a beta blocker or a calcium channel blocker) or an agent to control fluid and electrolyte balance, your doctor may need to adjust the dosage.

If you are diabetic, your doctor may need to adjust your insulin dosage.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Sandostatin LAR should only be used during pregnancy if clearly needed.

Women of child-bearing age should use an effective contraceptive method during treatment.

Do not breast-feed while using Sandostatin LAR. It is not known whether Sandostatin LAR passes into breast milk.

**Driving and using machines**

Sandostatin LAR has no or negligible effects on the ability to drive and use machines. However, some of the side effects you may experience while using Sandostatin LAR, such as headache and tiredness, may reduce your ability to drive and use machines safely.

**Sandostatin LAR contains sodium**

Sandostatin LAR contains less than 1 mmol sodium (23 mg) per dose, which means it is essentially “sodium-free”.

**3. How to use Sandostatin LAR**

Sandostatin LAR must always be administered as an injection into the muscle of the buttocks. With repeated administration, the left and right buttock should be used alternately.

**If you use more Sandostatin LAR than you should**

No life-threatening reactions have been reported after overdose of Sandostatin LAR.

The symptoms of overdose are: hot flushes, frequent urination, tiredness, depression, anxiety and lack of concentration.

If you think that an overdose has happened and you experience such symptoms, tell your doctor straight away.

**If you forget to use Sandostatin LAR**

If your injection is forgotten, it is recommended that you are given it as soon as it is remembered, and then continue as usual. It will not do any harm if a dose is a few days late, but you could get some temporary re-appearance of symptoms until you get back on schedule.

**If you stop using Sandostatin LAR**

If you interrupt your treatment with Sandostatin LAR your symptoms may come back. Therefore, do not stop using Sandostatin LAR unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious. Tell your doctor straight away if you get any of the following:**

**Very common** (may affect more than 1 in 10 people):

- Gallstones, causing sudden back pain.

- Too much sugar in the blood.

**Common** (may affect up to 1 in 10 people):

- Underactive thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight; tiredness, feeling cold, or swelling at the front of the neck.
- Changes in thyroid function tests.
- Inflammation of the gallbladder (cholecystitis); symptoms may include pain in the upper right abdomen, fever, nausea, yellowing of the skin and eyes (jaundice).
- Too little sugar in the blood.
- Impaired glucose tolerance.
- Slow heart beat.

**Uncommon** (may affect up to 1 in 100 people):

- Thirst, low urine output, dark urine, dry flushed skin.
- Fast heart beat.

**Other serious side effects**

- Hypersensitivity (allergic) reactions including skin rash.
- A type of an allergic reaction (anaphylaxis) which causes difficulty in breathing or dizziness.
- An inflammation of the pancreas gland (pancreatitis); symptoms may include sudden pain in the upper abdomen, nausea, vomiting, diarrhoea.
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine.
- Irregular heart beat.

Tell your doctor straight away if you notice any of the side effects above.

**Other side effects:**

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed below. They are usually mild and tend to disappear as treatment progresses.

**Very common** (may affect more than 1 in 10 people):

- Diarrhoea.
- Abdominal pain.
- Nausea.
- Constipation.
- Flatulence (wind).
- Headache.
- Local pain at the injection site.

**Common** (may affect up to 1 in 10 people):

- Stomach discomfort after meal (dyspepsia).
- Vomiting.
- Feeling of fullness in the stomach.
- Fatty stools.
- Loose stools.
- Discolouration of faeces.
- Dizziness.
- Loss of appetite.
- Change in liver function tests.
- Hair loss.
- Shortness of breath.
- Weakness.

If you get any side effects, please tell your doctor, nurse or pharmacist.

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Sandostatin LAR**

Keep this medicine out of the sight and reach of children.

Store in the original package in order to protect from light.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Sandostatin LAR may be stored below 25°C on the day of injection.

Do not store Sandostatin LAR after reconstitution (it must be used immediately).

Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

Do not use this medicine if you notice particles or a change of colour.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Sandostatin LAR contains**

- The active substances is octreotide  
One vial contains 10 mg, 20 mg or 30 mg octreotide (as octreotide acetate)
- The other ingredients are  
in powder (vial): poly(DL-lactide-co-glycolide), mannitol (E421).  
in solvent (prefilled syringe): carmellose sodium, mannitol (E421), poloxamer 188, water for injections.

### **What Sandostatin LAR looks like and contents of the pack**

Unit packs containing one 6 mL glass vial with rubber stopper (bromobutyl rubber), sealed with an aluminium flip-off seal, containing powder for suspension for injection and one 3 mL colourless pre-filled glass syringe with front and plunger stopper (chlorobutyl rubber) with 2 mL solvent, co-packaged in a sealed blister tray with one vial adapter and one safety injection needle.

Multipacks of three unit packs, each unit pack containing: one 6 mL glass vial with rubber stopper (bromobutyl rubber), sealed with an aluminium flip-off seal, containing powder for suspension for injection and one 3 mL colourless pre-filled glass syringe with front and plunger stopper (chlorobutyl rubber) with 2 mL solvent, co-packaged in a sealed blister tray with one vial adapter and one safety injection needle.

Not all strengths and pack sizes may be marketed in your country.

### **Marketing Authorisation Holder and Manufacturer**

[To be completed nationally]

**This medicinal product is authorised in the Member States of the EEA under the following names:**

Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Iceland, Latvia, Lithuania, Malta, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom	Sandostatin LAR
Belgium, Luxemburg, Netherlands	Sandostatine LAR
Italy, Portugal	Sandostatina LAR
France	Sandostatine L.P.

**This leaflet was last revised in {MM/YYYY}.**

[To be completed nationally]

The following information is intended for healthcare professionals only:

**How much Sandostatin LAR to use**

*Acromegaly*

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. If after 3 months, GH, IGF-1, and/or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF-1 serum concentrations normalised, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg Sandostatin LAR may be administered every 4 weeks. However, particularly in this group of patients, it is recommended to closely monitor adequate control of serum GH and IGF-1 concentrations, and clinical signs/symptoms at this low dose of Sandostatin LAR.

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

*Gastro-entero-pancreatic endocrine tumours*

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

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

- *Treatment of patients with advanced Neuroendocrine Tumours of the midgut or of unknown origin where non-midgut sites of origin have been excluded*

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

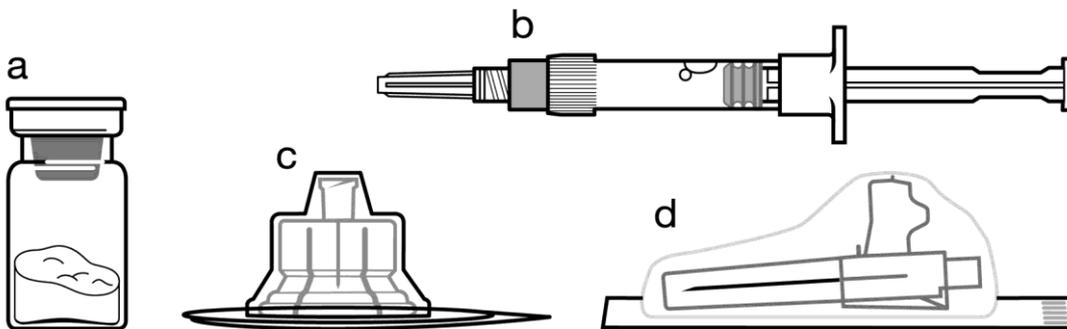
#### *Treatment of TSH-secreting adenomas*

Treatment with Sandostatin LAR should be started at a dose of 20 mg at 4-weekly intervals for 3 months before considering dose adjustment. The dose is then adjusted on the basis of the TSH and thyroid hormone response.

### **Instructions for preparation and intramuscular injection for Sandostatin LAR**

FOR DEEP INTRAMUSCULAR INJECTION ONLY

**Included in the injection kit:**



- One vial containing Sandostatin LAR powder,
- One prefilled syringe containing the vehicle solution for reconstitution,
- One vial adapter for drug product reconstitution,
- One safety injection needle.

Follow the instructions below carefully to ensure proper reconstitution of Sandostatin LAR before deep intramuscular 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.

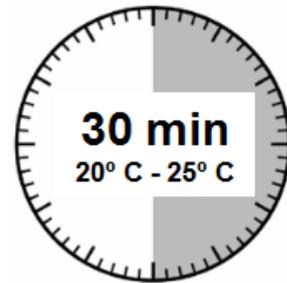
Sandostatin LAR should only be administered by a trained healthcare professional.

### 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.



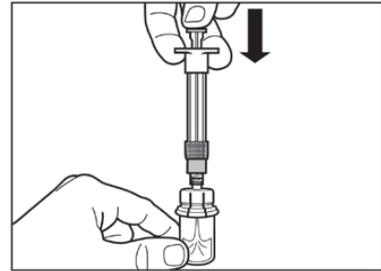
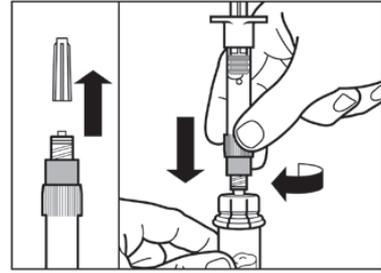
### Step 2

- 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 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.

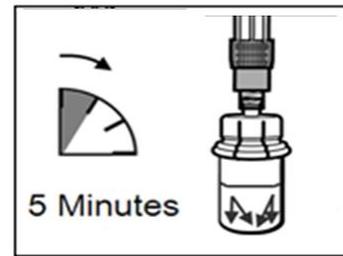


### Step 4

**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.

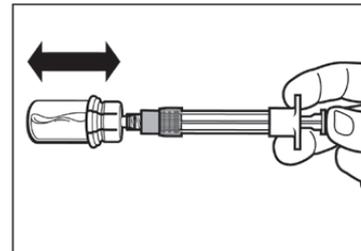
- At this stage prepare the patient for injection.



### Step 5

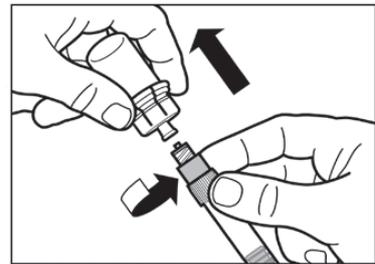
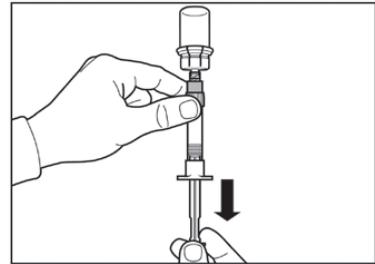
- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.

**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.**



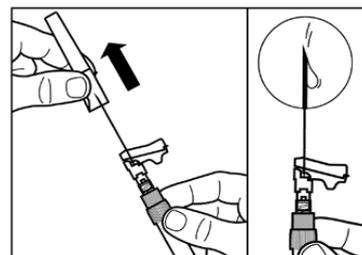
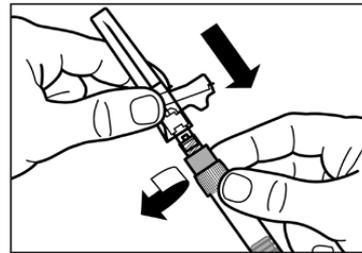
### Step 6

- 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.



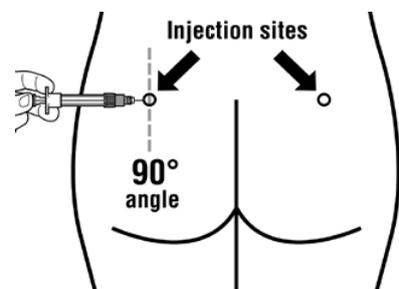
### Step 7

- Screw the safety injection needle onto the syringe.
- 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 intramuscular injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90° angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- 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 two 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).

