

Drug Regulatory Affairs

SANDOSTATIN[®] LAR[®]
(octreotide acetate)

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

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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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.

2 Qualitative and quantitative composition

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.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Powder and solvent for suspension for injection.

Powder: white to off-white powder [78].

Solvent for suspension for injection: clear, colourless solution [79].

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

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

4 Clinical particulars

4.1 Therapeutic indications

Treatment of patients with acromegaly [1,46]:

- *who are adequately controlled* on s.c. treatment with Sandostatin[®],
- *in whom* surgery or radiotherapy is inappropriate or ineffective [15,52-54], or in the interim period until radiotherapy becomes fully effective (see 4.2. Posology and method of administration).

Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumours *in whom symptoms are adequately controlled* on s.c. treatment with Sandostatin [47,48]:

Carcinoid tumours with features of the carcinoid syndrome.

VIPomas.

Glucagonomas.

Gastrinomas/Zollinger-Ellison syndrome.

Insulinomas, for pre-operative control of hypoglycaemia and for maintenance therapy.

GRFomas.

Treatment of patients with advanced Neuroendocrine Tumours of the midgut or unknown primary tumour location [81].

4.2 Posology and method of administration

Sandostatin LAR may only be administered by deep intragluteal injection. The site of repeat intragluteal injections should be alternated between the left and right gluteal muscle (see 6.6 Instructions for use/handling) [1].

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. Treatment with Sandostatin LAR can be started 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 [1-5].

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 [46].

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 [1].

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

For *patients in whom* surgery or radiotherapy is inappropriate or ineffective [15,52-54], or in the interim period until radiotherapy becomes fully effective, a short test dosing period of s.c. administration of Sandostatin is recommended to assess the response and systemic tolerability of octreotide prior to initiating treatment with Sandostatin LAR as described above [1].

Gastro-entero-pancreatic endocrine tumours [47]

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

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. The treatment with s.c. Sandostatin should be continued 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 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 unknown primary tumour location [81]

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

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 [6]. 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 [7]. Due to the wide therapeutic window of octreotide, no dose adjustment of Sandostatin LAR is necessary in patients with liver cirrhosis.

Use in the elderly

In a study with Sandostatin administered s.c., no dose adjustment was necessary in subjects \geq 65 years of age [8]. 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 [70,71].

4.3 Contraindications

Known hypersensitivity to octreotide or to any of the excipients, (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

General

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

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with octreotide (see also section 4.6 Pregnancy and lactation) [76].

Thyroid function should be monitored in patients receiving prolonged treatment with octreotide [76].

Cardiovascular related events

Uncommon cases of bradycardia have been reported. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary [72].

Gallbladder and related events

Development of gallstones has been reported in 15 to 30% of long-term recipients of s.c. Sandostatin [9,46,57-63]. The prevalence in the general population (aged 40 to 60 years) is about 5 to 20% [64]. 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 [46,47]. Ultrasonic examination of the gallbladder before and at about 6 monthly intervals during Sandostatin LAR therapy is however recommended [47]. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

(See page 16 'Recommendation for the management of patients during Sandostatin LAR treatment with respect to the development of gallstones'). [This section to be included ONLY as an advice, NOT COMPULSORY to include (depending on s.c. Sandostatin registration).]

Glucose metabolism

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

In patients with concomitant Type I diabetes mellitus, Sandostatin LAR is likely to affect glucose regulation, and insulin requirements may be reduced [65,66]. In non-diabetics and type II diabetics with partially intact insulin reserves, Sandostatin s.c. administration may result in

increases in post-prandial glycaemia [67]. 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 [49].

Nutrition

Octreotide may alter absorption of dietary fats in some patients [72].

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 [72].

4.5 Interaction with other medicinal products and other forms of interaction

Octreotide has been found to reduce the intestinal absorption of ciclosporin [13,14] and to delay that of cimetidine.

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine [15].

Limited published data [55,56] 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.

4.6 Pregnancy and lactation

Pregnancy [76]

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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development apart from some transient retardation of physiological growth (see section 5.3 Preclinical safety data).

Sandostatin should only be prescribed to pregnant women under compelling circumstances (see also section 4.4 Special warnings and precautions for use) [76].

Lactation [76]

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk [77]. Patients should not breast-feed during Sandostatin treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects [76]

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, localized pain, biliary sludge, thyroid dysfunction (e.g., decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycaemia [76].

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

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.

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 [18].

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 Special warnings and precautions for use) [73,75,76].

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 [73,76]

| | |
|--|---|
| Gastrointestinal disorders | |
| Very common: | Diarrhoea, abdominal pain, nausea, constipation, flatulence. |
| Common: | Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces. |
| Nervous system disorders | |
| Very common: | Headache. |
| Common: | Dizziness. |
| Endocrine disorders | |
| Common: | Hypothyroidism, thyroid dysfunction (e.g., decreased TSH, decreased Total T4, and decreased Free T4). |
| Hepatobiliary disorders | |
| Very common: | Cholelithiasis. |
| Common: | Cholecystitis, biliary sludge, hyperbilirubinaemia. |
| Metabolism and nutrition disorders | |
| Very common: | Hyperglycaemia [16]. |
| Common: | Hypoglycaemia [16], impaired glucose tolerance, anorexia. |
| Uncommon: | Dehydration. |
| General disorders and administration site | |
| Very common: | Injection site localized pain [1-5]. |
| Investigations | |
| Common: | Elevated transaminase levels. |
| Skin and subcutaneous tissue disorders | |
| Common: | Pruritus, rash, alopecia [17]. |
| Respiratory disorders | |
| Common: | Dyspnoea. |
| Cardiac disorders | |
| Common: | Bradycardia. |
| Uncommon: | Tachycardia. |

Post-marketing [76]

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 [76]

| | |
|---|--|
| Immune disorders | Anaphylaxis, allergy/hypersensitivity reactions [68,69]. |
| Skin and subcutaneous tissue disorders | Urticaria. |
| Hepatobiliary disorders | Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice. |
| Cardiac disorders | Arrhythmias. |
| Investigations | Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels. |

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 [76].

The management of overdosage is symptomatic.

5 Pharmacological properties

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

5.1 Pharmacodynamic properties

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* [1,9] 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).

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) [1,9].

In *patients with acromegaly*, Sandostatin LAR, a galenical formulation of octreotide suitable for repeated administration at intervals of 4 weeks, delivers consistent and therapeutic octreotide serum concentrations thus consistently lowering GH and normalising IGF 1 serum concentrations in the majority of patients. In most patients, Sandostatin LAR markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paraesthesia, fatigue, osteoarthralgia and carpal tunnel syndrome [1-5,46]. 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 [80].

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 [47,48]

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 [47,49]

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, computer tomography scanning suggests a slowing or arrest of progression of the tumour, or even tumour shrinkage, particularly of hepatic metastases. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas [47,49]

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 [47,49]

Although therapy with proton pump inhibitors or H₂-receptor blocking agents controls the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid, such control may be incomplete. Diarrhoea may also be a prominent symptom not alleviated in all patients by this therapy. Octreotide alone or in conjunction with proton pump inhibitors or H₂-receptor antagonists may reduce gastric acid hypersecretion and improve symptoms, including diarrhoea. Other symptoms possibly due to peptide production by the tumour, e.g. flushing, may also be relieved. Plasma gastrin levels fall in some patients.

Insulinomas [47,49]

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 tumours, glycaemic control may be improved even without concomitant sustained reduction in circulating insulin levels.

GRFomas [47,49]

These rare tumours are characterised 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.

Advanced Neuroendocrine Tumours of the midgut or unknown primary tumour location [81]

A Phase III, randomized, 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 randomized 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.

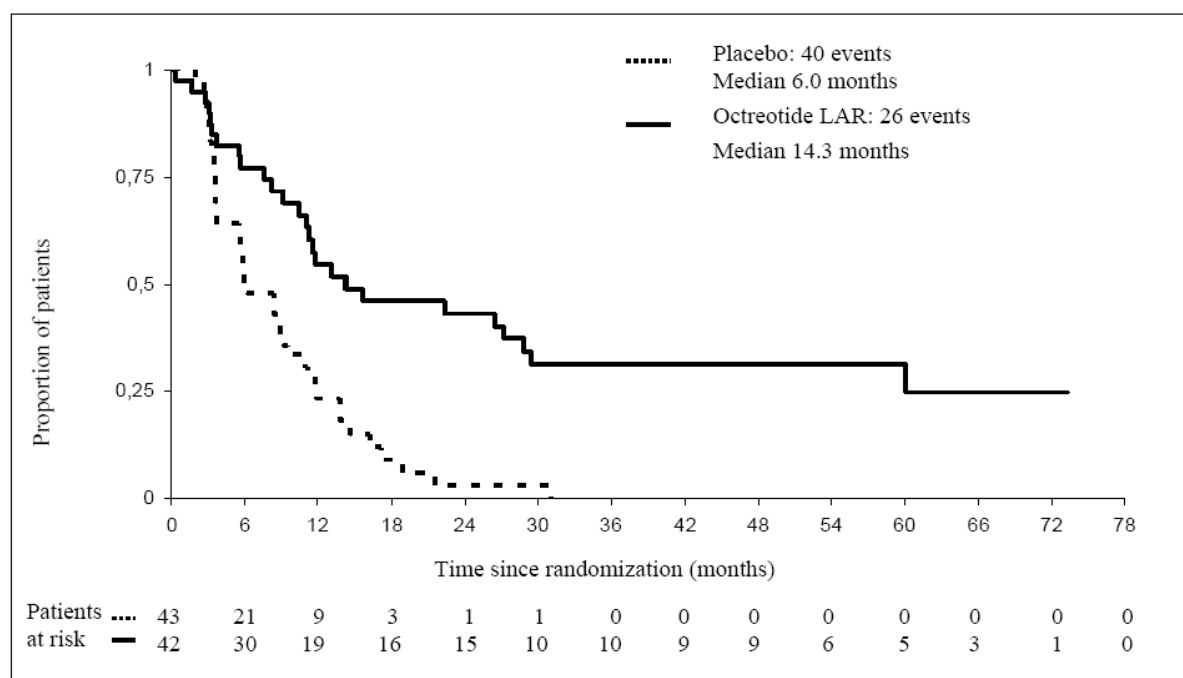
The primary endpoint was time to tumor progression or tumor-related death (TTP).

In the intent-to-treat analysis population (ITT) (all randomized 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 1 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 tumor 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.

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 [50]. 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 [50]. 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 [48].

No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR [50].

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.

5.3 Preclinical safety data

Acute toxicity [20-24]

Acute toxicity studies of octreotide in mice revealed LD₅₀ values of 72 mg/kg by the i.v. route and of 470 mg/kg by the s.c. route. The acute i.v. LD₅₀ value of octreotide in rats was determined at 18 mg/kg. Octreotide acetate was well tolerated by dogs receiving up to 1 mg/kg body weight by i.v. bolus injection.

Repeat dose toxicity [25-28]

In a repeat dose study performed in rats by i.m. injection of 2.5 mg Sandostatin LAR in 50 mg microspheres every 4 weeks for 21 weeks, with necropsy at 26 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. After a single i.m. injection of Sandostatin LAR in rats and rabbits, biodegradation of microspheres was complete by day 75 after injection in both species.

Mutagenicity [29-34]

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

Carcinogenicity/chronic toxicity [35-44]

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 98 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 tumours in rats are species-specific and are not relevant for the use of the drug in humans.

Reproduction toxicity [45]

Fertility as well as pre-, peri- and post-natal studies in female rats revealed no adverse effects on reproductive performance and development of the offspring, when s.c. doses of up to 1 mg/kg body weight per day were administered. Some retardation of the physiological growth noted in pups was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity.

6 Pharmaceutical particulars

6.1 List of excipients

Vial

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

Prefilled syringe

One **prefilled syringe** (solvent for parenteral use), containing: sodium carboxymethylcellulose 12.5 mg, mannitol 15 mg; water for injection qs ad 2.5 mL.

Information might differ in some countries.

6.2 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.

6.3 Shelf life

3 years [74].

Information might differ in some countries.

6.4 Special precautions for storage

Store at 2°C to 8°C (in a refrigerator). 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.

Information might differ in some countries.

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

6.5 Nature and contents of container

The microspheres are packaged in a 5 mL glass vial, with a Teflon-faced rubber stopper and sealed with an aluminium flip-off seal.

The vehicle is packaged in a pre-filled glass syringe which is closed with two rubber stoppers (a front and a plunger stopper).

Two needles [40 mm (1.5 inch), 19 gauge].

Country specific.

Special precautions for disposal

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

6.6 Instructions for use/handling

Select Instructions for use/handling for your local label as registered in your country.

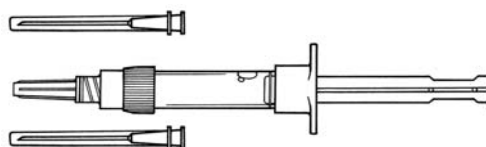
Instructions for intramuscular injection of Sandostatin LAR

FOR DEEP INTRAGLUTEAL INJECTION ONLY

Content:



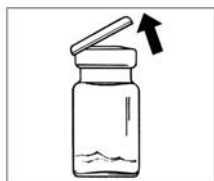
One vial containing
Sandostatin LAR



One prefilled syringe containing vehicle solution
+ two needles

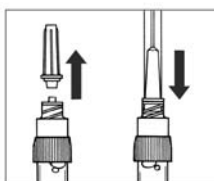
Follow the instructions below carefully to ensure complete saturation of the powder and its uniform suspension before i.m. injection.

Sandostatin LAR suspension must only be prepared **immediately** before administration. Sandostatin LAR should only be administered by a trained health professional.



Allow the Sandostatin LAR vial and the vehicle syringe to reach room temperature.

Remove the cap from vial containing Sandostatin LAR. Assure that the powder is settled at the bottom of the vial by lightly tapping the vial.



Remove the cap from the vehicle syringe.

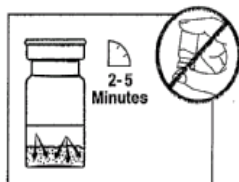
Attach one of the supplied needles to the vehicle syringe.



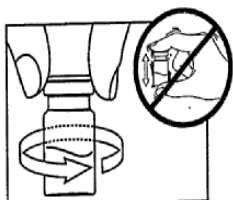
Disinfect the rubber stopper of the vial with an alcohol swab. Insert the needle through the centre of the rubber stopper of the Sandostatin LAR vial.



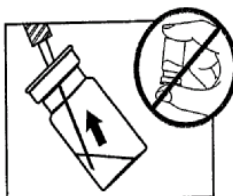
Without disturbing the Sandostatin LAR powder, gently inject all the vehicle into the vial by running the vehicle down the inside wall of the vial. Do not inject the vehicle directly into the powder. Withdraw the needle from the vial.



Do not disturb the vial until the vehicle has totally wetted the Sandostatin LAR powder (between 2 to 5 minutes). **Without inverting the vial** check the powder on the walls and bottom of the vial. If dry spots exist, allow undisturbed wetting to continue. At this stage, prepare the patient for injection.



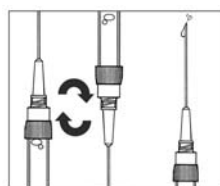
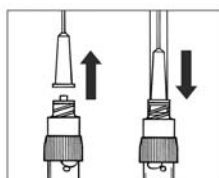
Once complete wetting has occurred, the vial should be moderately swirled for about 30 to 60 seconds until a uniform milky suspension is achieved. **Do not vigorously shake the vial** as this may cause the suspension to flocculate, making it unusable.



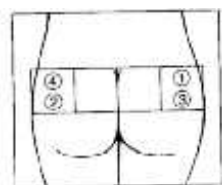
Immediately re-insert the needle through the rubber stopper and then, with the bevel down and the vial tipped at approximately 45 degree angle, slowly draw the contents of the vial into the syringe. **Do not invert the vial** when filling the syringe as this may affect the amount withdrawn.

It is normal for a small amount of suspension to remain on the walls and bottom of the vial. This is a calculated overfill.

Immediately change the needle (supplied).



Administration must occur immediately after the suspension has been prepared. Gently invert the syringe as needed to maintain a uniform suspension. Eliminate air from syringe.



Disinfect the injection site with an alcohol swab.

Insert needle into right or left gluteus and draw back to ensure that no blood vessel has been penetrated. Inject slowly i.m. by deep intragluteal injection with steady pressure. If the needle blocks, attach a new needle of the same diameter [1.1 mm, 19 gauge].

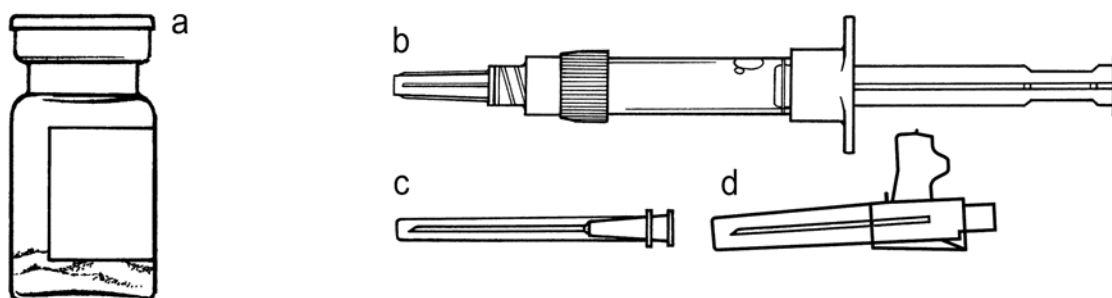
Sandostatin LAR must be given only by deep intragluteal injection, never i.v. If a blood vessel has been penetrated, attach a new needle and select another injection site.

Safety needle for injection: Instructions for use

Instructions for preparation and intramuscular injection of Sandostatin LAR

FOR DEEP INTRAGLUTEAL INJECTION ONLY

Content



- a One vial containing Sandostatin LAR
- b One prefilled syringe containing the vehicle solution for reconstitution
- c One 19G x 1.5" standard needle for transfer and drug product reconstitution
- d One 19G x 1.5" safety injection needle

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

Sandostatin LAR suspension must only be prepared **immediately** before administration. Sandostatin LAR should only be administered by a trained health professional.

Step 1

Before handling the component, allow the drug product vial and the vehicle syringe to reach room temperature and wash your hands with soap and hot water.

Place the package on a clean and flat surface.

Detach the flip off cap from the vial containing the drug product.

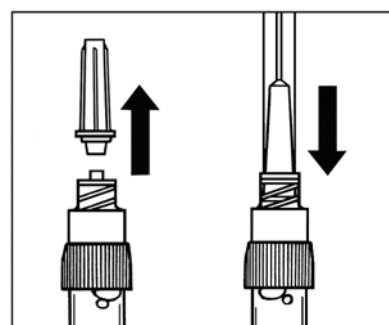
Assure that the powder is settled at the bottom of the vial by lightly tapping the vial.



Step 2

Remove the cap from the vehicle syringe and attach the **standard needle “c”** supplied for reconstitution.

Note: **Make sure not to use the safety injection needle** at this stage.



Step 3

Clean the rubber stopper of the vial with an alcohol swab.

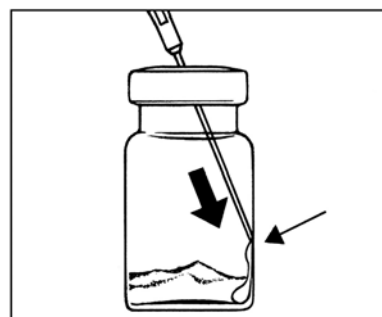
Insert the needle through the centre of the rubber stopper of the Sandostatin LAR vial.



Step 4

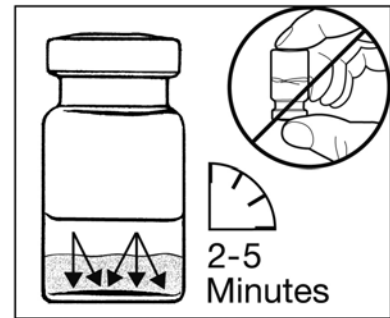
Without disturbing the Sandostatin LAR powder, gently inject the vehicle into the vial by running the vehicle down the inside wall of the vial. Do not inject the vehicle directly into the powder.

Withdraw the needle from the vial. To avoid contamination please make sure not to expose the needle to surfaces.



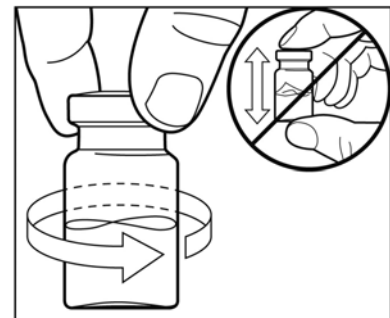
Step 5

Do not disturb the vial until the vehicle has totally wetted the Sandostatin LAR powder (between 2 to 5 minutes). **Without inverting the vial** check the powder on the walls and bottom of the vial. If dry spots exist, allow undisturbed wetting to continue. At this stage, prepare the patient for injection.



Step 6

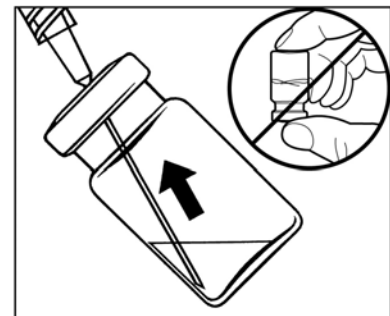
Once complete wetting has occurred, the vial should be moderately swirled for about 30 to 60 seconds until a uniform milky suspension is achieved. **Do not vigorously shake the vial** as this may cause the suspension to flocculate, making it unusable.



Step 7

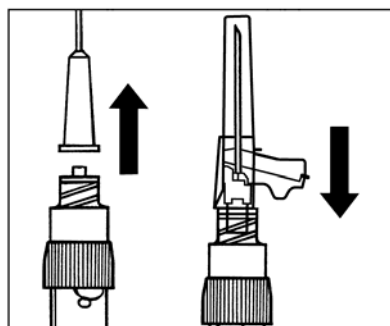
Immediately re-insert the needle through the rubber stopper and then, with the bevel down and the vial tipped at approximately 45 degree angle, slowly draw the contents of the vial into the syringe. **Do not invert the vial** when filling the syringe as this may affect the amount withdrawn.

It is normal for a small amount of suspension to remain on the walls and bottom of the vial. This is a calculated overfill.



Step 8

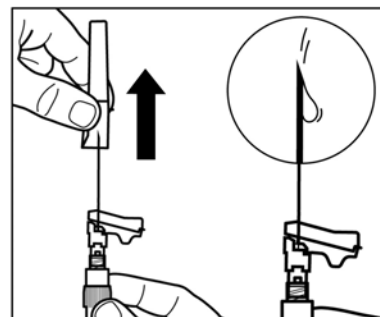
Remove the needle for transfer from the syringe and immediately attach the safety injection needle to the syringe.



Step 9

Remove the protective needle cover, gently invert the syringe as needed to maintain a uniform suspension and expel any air from the syringe.

The drug is now ready for administration. The administration must occur immediately after the suspension has been prepared.

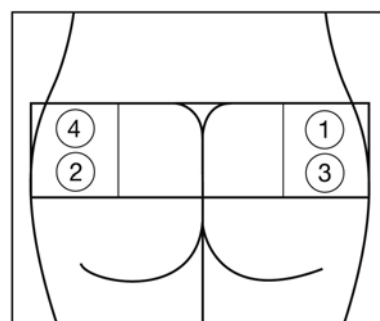


Step 10

Clean the injection site with an alcohol swab.

Insert needle into the right or left gluteus and draw back to ensure that no blood vessel has been penetrated. Inject slowly i.m. by deep intragluteal injection with steady pressure.

Sandostatin LAR must be given only by deep intragluteal injection, never i.v.



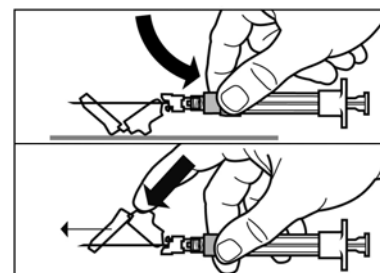
Step 11

Using a single handed operation, activate the safety system of the needle

- either with help of a rigid surface, e.g. table
- or with a finger, e.g. forefinger making sure always to keep all fingers behind the needle tip.

An audible “clic” confirms the proper activation of the safety mechanism.

Immediately dispose of properly all packaging and devices implemented for the preparation and administration of the drug product into an approved sharp 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) [59] 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.

This is a non-referenced document.