מרץ 2020

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : <u>עדכוני עלוני התכשיר</u>

<u>Sandostatin® LAR® 10 mg powder and solvent for suspension for injection</u>

<u>סנדוסטטין LAR® 10 מ"ג אבקה וממס להכנת תרחיף להזרקה</u>

<u>Sandostatin® LAR® 20 mg powder and solvent for suspension for injection</u>

<u>סנדוסטטין LAR® 20 מ"ג אבקה וממס להכנת תרחיף להזרקה</u>

<u>Sandostatin® LAR® 30 mg powder and solvent for suspension for injection</u>

<u>סנדוסטטין LAR® 30 מ"ג אבקה וממס להכנת תרחיף להזרקה</u>

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לצרכן ועלון לרופא של התכשירים שבנדון.
העלונים לרופא ולצרכן עודכנו במרץ 2020.

פורמט העלונים עודכן. העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום: נוברטיס ישראל בע"מ, תוצרת הארץ 6, ת.ד. 7126, תל אביב

<u>לתשומת לבכם</u>, העלונים המעודכנים כוללים הוראות הכנה והזרקה עבור פרזנטציית תכשיר חדשה.
פרזנטציית תכשיר מעודכנת כוללת אביזרים נלווים והרכב ממס חדשים. שיווק הפרזנטציה החדשה יתחיל עד סוף שנת 2020. שאר המידע בעלונים נכון גם עבור הפרזנטציה המשווקת היום.

התוויות התכשיר:

Treatment of acromegaly in: Patients already adequately controlled on standard doses of sandostatin s.c. Patients in whom surgery or radiotherapy are inappropriate or ineffective, or who are in the latency period before radiotherapy becomes fully effective.

Endocrine Gastro-Entero-Pancreatic (GEP) tumors, carcinoid tumors

חומר פעיל:
כל בקבוקון אבקה מכיל : 10 מ"ג, 20 מ"ג או 30 מ"ג אוקטראוטיד (כאוקטראוטיד אצטט)
10 mg, 20 mg or 30 mg octreotide (as octreotide acetate)

נוברטיס ישראל בע"מ.
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עלון לרופא:

עלון בפורמט חדש
העדכונים המהווים עדכון במידע בטיחותי מודגשים בצהוב

Prescribing Information

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

One vial contains 10 mg, 20 mg or 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: Colourless to slightly yellow or brown solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of acromegaly in: Patients already adequately controlled on standard doses of sandostatin s.c. Patients in whom surgery or radiotherapy are inappropriate or ineffective, or who are in the latency period before radiotherapy becomes fully effective.

Endocrine Gastro-Entero-Pancreatic (GEP) tumors, carcinoid tumors.

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).

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Posology

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.

For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF 1) are not fully controlled (GH concentrations still above 2.5 microgram/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF 1 serum concentrations 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.

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

Gastro-entero-pancreatic endocrine 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 LAR every 4 weeks.

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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.

Special populations

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

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

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

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

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.

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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

Cholelithiasis is a very common event during Sandostatin treatment and may be associated with cholecystitis and biliary duct dilatation (see section 4.8). Ultrasonic examination of the gallbladder before and at about 6-monthly intervals during Sandostatin LAR therapy is recommended.

Glucose metabolism

Because of its inhibitory action on growth hormone, glucagon, and insulin release, Sandostatin LAR may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with s.c. Sandostatin, in some instances, 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).

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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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥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.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Endocrine disorders	
Common:	Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased total T4, and decreased free T4).
Hepatobiliary disorders	
Very common:	Cholelithiasis.
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia.

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Metabolism and nutrition disorders	
Very common:	Hyperglycaemia.
Common:	Hypoglycaemia, impaired glucose tolerance, anorexia.
Uncommon:	Dehydration.
General disorders and administration site conditions	
Very common:	Injection site reactions.
Common:	Asthenia.
Investigations	
Common:	Elevated transaminase levels.
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
Respiratory disorders	
Common:	Dyspnoea.
Cardiac disorders	
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

Blood and lymphatic system disorders Thrombocytopenia
Immune system disorders Anaphylaxis, allergy/hypersensitivity reactions.
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.

Description of selected adverse reactions
Gallbladder and related reactions
Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Development of gallstones has been reported in 15 to 30% of long-term recipients of s.c. Sandostatin. The incidence in the general population (aged 40 to 60 years) is about 5 to 20%. Long-term exposure to Sandostatin LAR of patients with acromegaly or gastro-entero-pancreatic tumors suggests that treatment with Sandostatin LAR does not increase the incidence of gallstone formation, compared with s.c. treatment. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

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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.

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

Injection site reactions
Injection site related reactions including pain, redness, haemorrhage, pruritus, swelling or induration 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
Bradycardia is a common adverse reaction with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early 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).

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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 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. 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 H2 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 H2 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 inoperative 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.

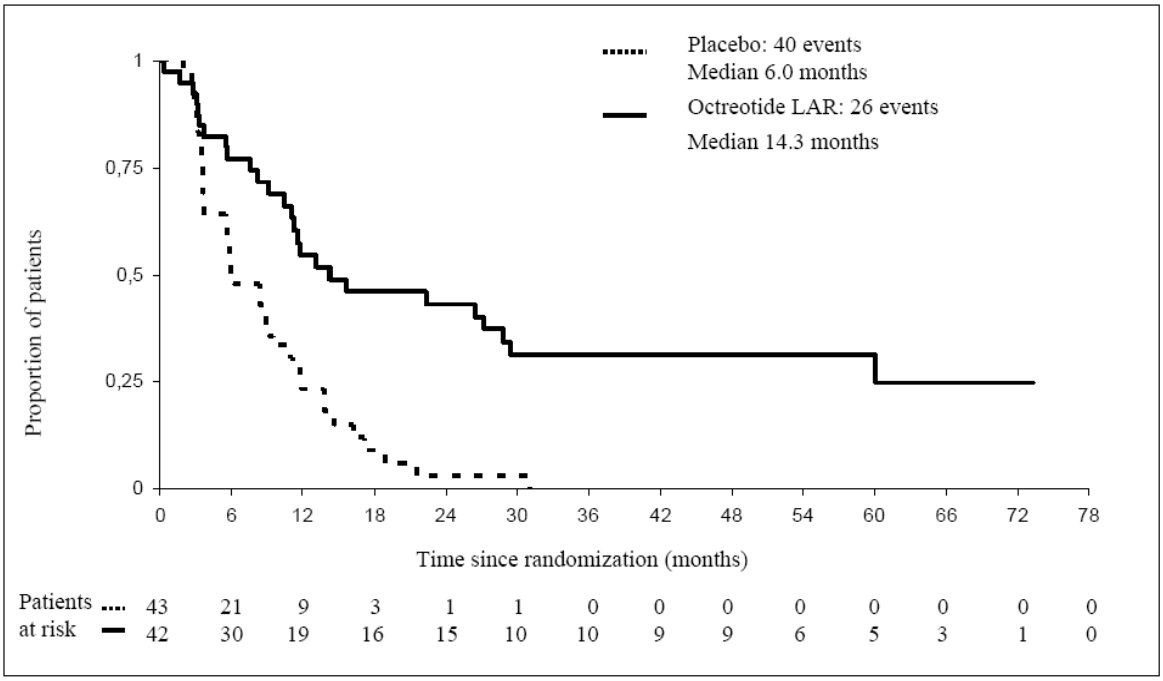
The primary endpoint was time to tumour progression or tumour-related death (TTP).

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]

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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 67% of patients in the Sandostatin LAR group and 37% of patients in the placebo group.

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

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

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)
Sterilized Mannitol

Solvent (Prefilled syringe):
Carmellose sodium
Mannitol
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

The expiry date of the product is indicated on the packaging materials.
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 rigid plastic tray with one vial adapter and one safety injection needle.

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.

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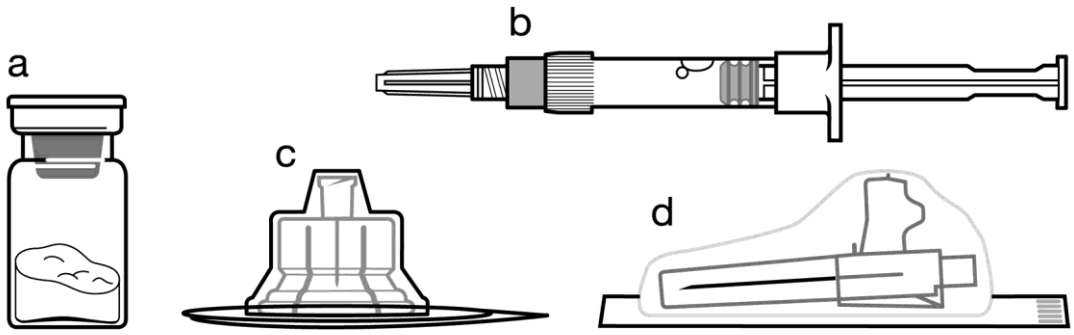
Instructions for preparation and intramuscular injection for Sandostatin LAR

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.

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Step 1

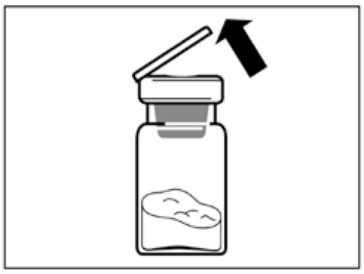
- Remove the Sandostatin LAR injection kit from refrigerated storage.

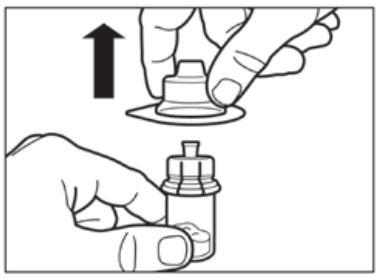
  ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

  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.





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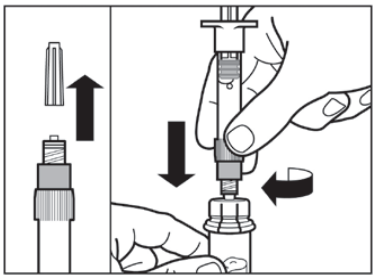
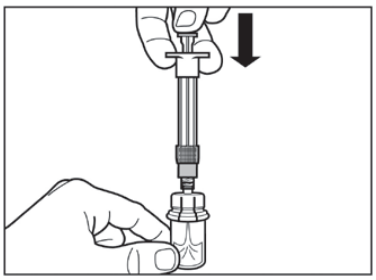
Step 3

- 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.



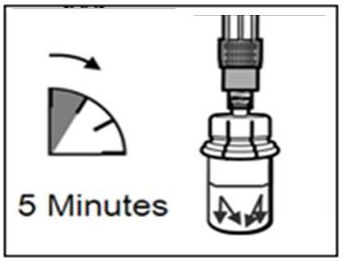


Step 4

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.

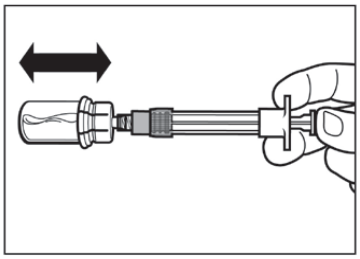
- At this stage prepare the patient for injection.



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.**



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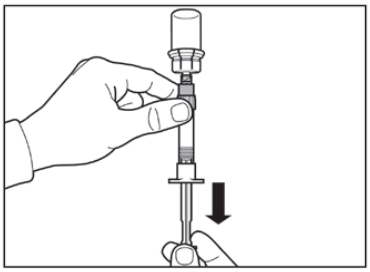
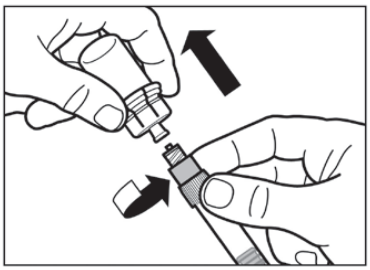
Step 6

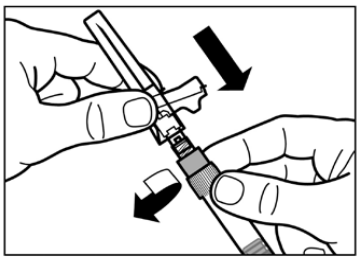
- Turn syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe.
- Unscrew the syringe from the vial adapter.

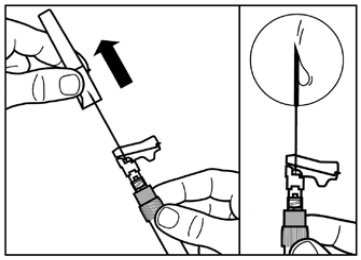




Step 7

- 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.





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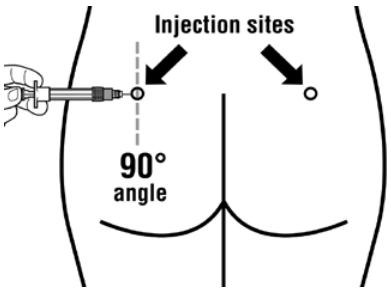
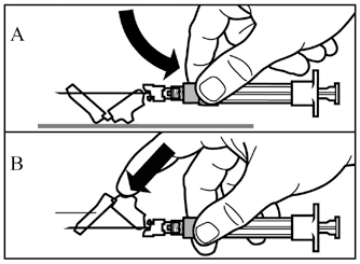
Step 8

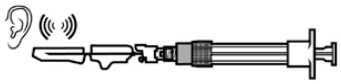
- Sandostatin LAR must be given only by deep intramuscular injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90º angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).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



Step 9

- Activate the safety guard over the needle in one of the 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. MANUFACTURER

Novartis Pharma Stein AG, Stein, Switzerland
for: Novartis Pharma AG, Basel, Switzerland

8. REGISTRATION HOLDER

Novartis Israel Ltd.,
P.O.B 7126, Tel Aviv, Israel

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עלון לרופא:

עלון חדש – עד כה הוצג בפורמט עלון לרופא

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו - 1986
התרופה משווקת על פי מרשם רופא בלבד

סנדוסטטין LAR® 10 מ"ג אבקה וממס להכנת תרחיף להזרקה
החומר הפעיל וכמותו:
כל בקבוקון אבקה מכיל אוקטראוטיד (כאוקטראוטיד אצטט) 10 מ"ג
octreotide (as octreotide acetate) 10 mg

סנדוסטטין LAR® 20 מ"ג אבקה וממס להכנת תרחיף להזרקה
החומר הפעיל וכמותו:
כל בקבוקון אבקה מכיל אוקטראוטיד (כאוקטראוטיד אצטט) 20 מ"ג
octreotide (as octreotide acetate) 20 mg

סנדוסטטין LAR® 30 מ"ג אבקה וממס להכנת תרחיף להזרקה
החומר הפעיל וכמותו:
כל בקבוקון אבקה מכיל אוקטראוטיד (כאוקטראוטיד אצטט) 30 מ"ג
octreotide (as octreotide acetate) 30 mg

חומרים בלתי פעילים ואלרגנים: ראה פרק 6 "מידע נוסף". ראה גם סעיף "מידע חשוב על חלק מהמרכיבים של התרופה".

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה עבורך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מצבם הרפואי דומה.

1. למה מיועדת התרופה?

סנדוסטטין LAR מיועדת ל:

- טיפול באנשים עם אקרומגליה:
  - שמחלתם נשלטת במידה מספקת על ידי טיפול במינונים סטנדרטיים של סנדוסטטין במתן תת-עורי
  - כאשר ניתוח או רדיותרפיה אינם מתאימים או שאינם יעילים
  - כדי לתת כיסוי בתקופת הביניים עד שהרדיותרפיה משיגה את יעילותה במלואה

- טיפול בגידולים אנדוקריניים בקיבה, מעיים ולבלב, גידולי קרצינואיד
(Endocrine Gastro-Entero-Pancreatic (GEP) tumors, carcinoid tumors)

קבוצה תרפויטית:
אנלוגים לסומטוסטטין

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סנדוסטטין LAR היא תרכובת סינתטית הנגזרת מסומטוסטטין. סומטוסטטין נמצא בדרך כלל בגוף האדם, בו הוא מעכב שחרור של הורמונים מסוימים כגון הורמון גדילה. לסנדוסטטין LAR יתרונות על סומטוסטטין, היא חזקה יותר והשפעותיה ארוכות יותר.

אקרומגליה הוא מצב שבו הגוף מייצר עודף של הורמון גדילה. הורמון הגדילה באופן רגיל מווסת גדילה של רקמות, איברים ועצמות. עודף בהורמון גדילה גורם לעלייה בגודל העצמות והרקמות, במיוחד בכפות הידיים והרגליים.
סנדוסטטין LAR מפחיתה באופן משמעותי את התסמינים של אקרומגליה, הכוללים כאב ראש, הזעת יתר, חוסר תחושה בכפות הידיים והרגליים, עייפות וכאב במפרקים.

ייצור מוגבר של הורמונים ספציפיים וחומרים אחרים יכול להיגרם על ידי כמה מצבים נדירים בקיבה, במעיים או בלבלב. זה מערער את האיזון ההורמונלי הטבעי של הגוף ומביא למגוון של תסמינים כגון הסמקה, שלשול, לחץ דם נמוך, פריחה וירידה במשקל. טיפול עם סנדוסטטין LAR מסייעת לשלוט בתסמינים אלה.

2. <u>לפני השימוש בתרופה</u>

עקוב אחרי כל הוראות הרופא שלך בקפדנות. הן עשויות להיות שונות מהמידע המופיע בעלון זה.

קרא את ההסברים הבאים לפני השימוש בסנדוסטטין LAR.

X אין להשתמש בתרופה אם:
אתה רגיש (אלרגי) לאוקטראוטיד או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (ראה פרק 6 "מידע נוסף").

אזהרות מיוחדות הנוגעות לשימוש בתרופה

! לפני הטיפול בסנדוסטטין LAR, ספר לרופא אם:
- אתה יודע שיש לך כעת אבני מרה, או שהיו לך בעבר; מאחר ששימוש ממושך בסנדוסטטין LAR עלול לגרום להיווצרות אבן מרה. ייתכן שהרופא שלך ירצה לבדוק את כיס המרה שלך באופן תקופתי.
- אתה יודע שיש לך סוכרת; מאחר שסנדוסטטין LAR עלולה להשפיע על רמות הסוכר בדם. אם אתה סוכרתי, יש לבדוק את רמות הסוכר שלך באופן קבוע.
- יש לך היסטוריה של מחסור בוויטמין B12; ייתכן שהרופא שלך ירצה לבדוק את רמת הוויטמין B12 שלך באופן תקופתי.

! ילדים ומתבגרים
קיים ניסיון מועט בשימוש בסנדוסטטין LAR בילדים.

! בדיקות ומעקב
אם אתה מקבל טיפול בסנדוסטטין LAR במשך תקופה ארוכה, ייתכן שהרופא שלך ירצה לבדוק את תפקוד בלוטת התריס שלך באופן תקופתי.

הרופא שלך יבדוק את תפקוד הכבד שלך.

! אינטראקציות/ תגובות בין תרופתיות
אם אתה לוקח או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

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באופן כללי אתה יכול להמשיך לקחת תרופות אחרות בזמן הטיפול בסנדוסטטין LAR. עם זאת, תרופות מסוימות, כגון סימטידין (cimetidine), ציקלוספורין (cyclosporin), ברומוקריפטין (bromocriptine), קווינידין (quinidine) וטרפנאדין (terfenadine) דווחו כמושפעות מסנדוסטטין LAR.

אם אתה לוקח תרופה על מנת לווסת את לחץ הדם שלך (למשל חוסם ביתא או חוסם תעלות סידן) או לוקח תכשיר על מנת לווסת את איזון נוזלים ואלקטרוליטים, ייתכן שהרופא שלך יצטרך להתאים את המינון.

אם אתה חולה סוכרת, ייתכן שהרופא שלך יצטרך להתאים את מינון האינסולין שלך.

! היריון, הנקה ופוריות
אם את בהיריון או מיניקה, חושבת שאת בהיריון או מתכננת להרות, היוועצי ברופא שלך לפני לקיחת תרופה זו.

יש להשתמש בסנדוסטטין LAR במהלך ההיריון רק אם יש בכך צורך ברור.

על נשים בגיל הפוריות להשתמש באמצעי מניעה יעיל במהלך הטיפול.
אין להניק במהלך הטיפול בסנדוסטטין LAR. לא ידוע אם סנדוסטטין LAR עוברת לחלב אם.

! נהיגה ושימוש במכונות
לסנדוסטטין LAR אין השפעות, או שהינן זניחות, על היכולת לנהוג ולהשתמש במכונות. עם זאת, חלק מתופעות הלוואי שאתה עלול לחוות תוך שימוש בסנדוסטטין LAR, כגון כאב ראש ועייפות, עלולות להפחית את היכולת שלך לנהוג ולהשתמש במכונות באופן בטוח.
באשר לילדים, יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת הכביש וכדומה.

! מידע חשוב על חלק מהמרכיבים של התרופה
סנדוסטטין LAR מכילה פחות מ 1 מילימול (mmol) נתרן (23 מ"ג) לכל מנה, כלומר היא למעשה "נטולת נתרן".

3. <u>כיצד תשתמש בתרופה?</u>

יש להשתמש בתרופה תמיד בהתאם להוראות הרופא.
עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.
המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.
אין לעבור על המנה המומלצת.
סנדוסטטין LAR חייבת להינתן תמיד כזריקה לתוך שריר העכוז. במתן חוזר יש להשתמש לסרוגין בעכוז השמאלי והימני.
התרופה תוזרק על-ידי צוות רפואי מיומן בלבד.

אם נטלת בטעות מינון גבוה יותר
לא דווחו תגובות מסכנות חיים לאחר מנת יתר של סנדוסטטין LAR.
התסמינים של מנת יתר הם: גלי חום, השתנה תכופה, עייפות, דיכאון, חרדה וחוסר ריכוז.
אם אתה חושב שקבלת מנת יתר ואתה חווה תסמינים כאלה, ספר לרופא שלך מייד.
אם בטעות התרופה הוזרקה לילד, פנה מייד לרופא או לחדר מיון של בית חולים, והבא אריזת התרופה איתך.

אם שכחת ליטול את התרופה
אם שכחת לקבל זריקה בזמן הדרוש, מומלץ לקבלה בהקדם האפשרי כשאתה נזכר, ולאחר מכן להמשיך כרגיל.
לא יגרם נזק אם המנה ניתנה באיחור של כמה ימים, אבל חלק מהתסמינים עלולים להופיע אצלך מחדש באופן זמני עד שתחזור לתכנית הטיפולים הרגילה.

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יש להתמיד בטיפול כפי שהומלץ על-ידי הרופא.
גם אם חל שיפור במצב בריאותך, אין להפסיק את הטיפול בתרופה ללא התייעצות עם הרופא.

אם אתה מפסיק את נטילת התרופה
אם אתה מפסיק את הטיפול שלך עם סנדוסטטין LAR, התסמינים שלך עשויים לחזור. לכן, אין להפסיק להשתמש בסנדוסטטין LAR אלא אם כן הרופא שלך יורה לך.

אין ליטול תרופות בחושך! בדוק התווית והמנה <u>בכל פעם</u> שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.
אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא, ברוקח או באחות שלך.

4. <u>תופעות לוואי</u>

כמו בכל תרופה, השימוש בסנדוסטטין LAR עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן שלא תסבול מאף אחת מהן.

תופעות לוואי מסויימות עלולות להיות רציניות. ספר לרופא שלך מייד אם אתה חווה כל אחת מהתופעות הבאות:

תופעות לוואי שכיחות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה)
- אבני מרה, עלולות לגרום לכאב גב פתאומי;
- יותר מדי סוכר בדם.

תופעות לוואי שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100)
- תת פעילות של בלוטת התריס (היפותירואידיזם) הגורמת לשינויים בקצב הלב, בתיאבון או במשקל, עייפות, תחושת קור או נפיחות בחלק הקדמי של הצוואר;
- שינויים בבדיקות תפקוד בלוטת התריס;
- דלקת של כיס המרה (כולסטיטיס): התסמינים עשויים לכלול כאב בבטן הימנית העליונה, חום, בחילה, הצהבה של העור והעיניים (צהבת);
- פחות מדי סוכר בדם;
- ליקוי בסבילות לגלוקוז;
- קצב לב איטי.

תופעות לוואי שאינן שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000)
- צמא, ירידה בתפוקת שתן, שתן כהה, עור יבש וסמוק;
- קצב לב מהיר.

תופעות לוואי חמורות אחרות
- תגובות של רגישות יתר (אלרגיה) כולל פריחה בעור;
- סוג של תגובה אלרגית (אנפילקסיס) היכולה לגרום לקושי בבליעה או בנשימה, נפיחות ועקצוץ, ייתכן עם ירידה בלחץ הדם עם סחרחורת או איבוד הכרה;
- דלקת בבלוטת הלבלב (פנקריאטיטיס): התסמינים יכולים לכלול כאב פתאומי בבטן העליונה, בחילה, הקאה, שלשול;
- דלקת כבד (הפטיטיס): התסמינים יכולים לכלול הצהבה של העור והעיניים (צהבת), בחילה, הקאה, אובדן תיאבון, תחושה כללית לא טובה, גרד, שתן בצבע בהיר;
- קצב לב לא סדיר;
- ספירה נמוכה של טסיות בדם: עלול לגרום לדימום מוגבר או לחבורות.

ספר לרופא שלך מייד אם אתה מבחין באחת מתופעות הלוואי לעיל.

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תופעות לוואי אחרות:
דווח לרופא, לרוקח או לאחות שלך אם אתה מבחין באחת מתופעות הלוואי המפורטות להלן. הן בדרך כלל מתונות ונוטות להיעלם עם התקדמות הטיפול.

תופעות לוואי שכיחות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה)
- שלשול;
- כאב בטן;
- בחילה;
- עצירות;
- הצטברות גזים במערכת העיכול;
- כאב ראש;
- כאב מקומי באזור ההזרקה.

תופעות לוואי שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100)
- אי נוחות בבטן לאחר ארוחה (דיספפסיה);
- הקאה;
- תחושת מלאות בבטן;
- צואה שומנית;
- צואה דלילה;
- שינוי בצבע הצואה;
- סחרחורת;
- אובדן תיאבון;
- שינוי בבדיקות תפקודי כבד;
- נשירת שיער;
- קוצר נשימה;
- חולשה.

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם הרופא.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור: https://sideeffects.health.gov.il/

5. <u>איך לאחסן את התרופה?</u>

מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.

אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה.
תאריך התפוגה מתייחס ליום האחרון של אותו חודש.

תנאי אחסון:
יש לאחסן במקרר (2-8°C).
אין להקפיא.
יש לאחסן באריזה המקורית על מנת להגן מאור.
ניתן לאחסן סנדוסטטין LAR מתחת ל 25°C ביום ההזרקה.

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יש להשתמש מייד לאחר שחזור.

אין להשתמש בתרופה זו אם אתה מבחין בחלקיקים או בשינוי צבע.

אין להשליך תרופות לביוב או לפסולת ביתית. יש להיוועץ ברוקח היכן ניתן להשליך תרופות שאינן בשימוש. צעדים אלו יסייעו להגן על הסביבה.

6. <u>מידע נוסף</u>

נוסף על המרכיב הפעיל התרופה מכילה גם:
אבקה (בקבוקון):
Poly (DL-lactide-co-glycolide) and sterilized mannitol
ממס (מזרק מוכן לשימוש):
Carmellose sodium, mannitol, poloxamer 188, water for injections

כיצד נראית התרופה ומה תוכן האריזה:

האבקה היא בצבע לבן עד לבן מעט צהבהב בבקבוקון. הממס הוא נטול צבע עד צהוב בהיר או חום בהיר במזרק מוכן לשימוש.

כל אריזה מכילה:
- בקבוקון זכוכית אחד של 6 מ"ל עם פקק גומי אטום עם סוגר אלומיניום, המכיל אבקה להכנת תרחיף להזרקה
- מזרק אחד של 3 מ"ל מוכן לשימוש מזכוכית נטולת צבע עם פקק קדמי ופקק בוכנה מגומי המכיל 2 מ"ל ממס
- הבקבוקון והמזרק ארוזים יחד במגש פלסטיק קשיח עם מתאם בקבוקון אחד ומחט בטיחותית אחת להזרקה.

בעל הרישום:
נוברטיס ישראל בע"מ, ת.ד. 7126, תל- אביב.

יצרן:
נוברטיס פארמה שטיין איי ג'י, שטיין, שוויץ עבור נוברטיס פארמה איי ג'י, בזל, שוויץ.

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו עודכן בהתאם להוראות משרד הבריאות בתאריך מרץ 2020.

מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:
סנדוסטטין LAR 10 מ"ג: 112 50 29488
סנדוסטטין LAR 20 מ"ג: 112 49 29489
סנדוסטטין LAR 30 מ"ג: 112 48 29490

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.

המידע הבא מיועד לאנשי הצוות הרפואי בלבד:

The following information is intended for healthcare professionals only:

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How much Sandostatin LAR to use

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.

For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF 1) are not fully controlled (GH concentrations still above 2.5 microgram/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 microgram/L, whose IGF 1 serum concentrations 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.

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

Gastro-entero-pancreatic endocrine 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 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.

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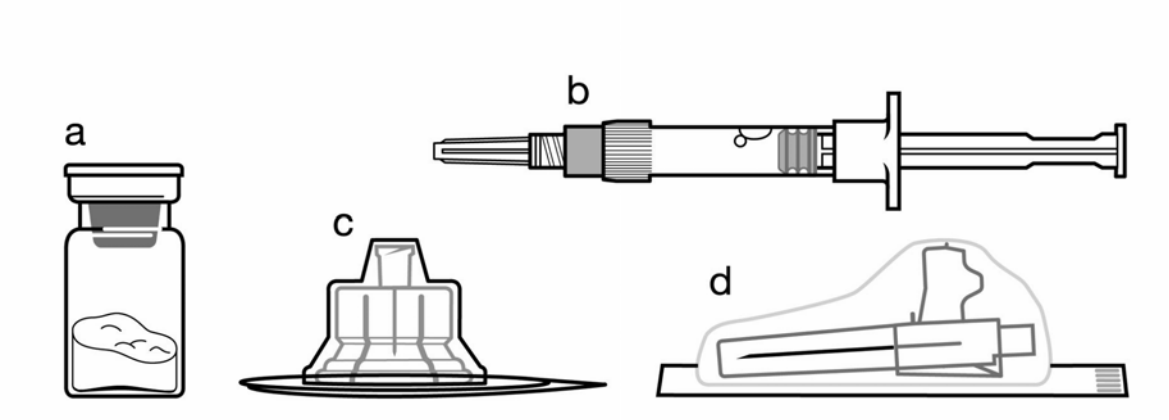
Instructions for preparation and intramuscular injection for Sandostatin LAR

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

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.

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Step 1

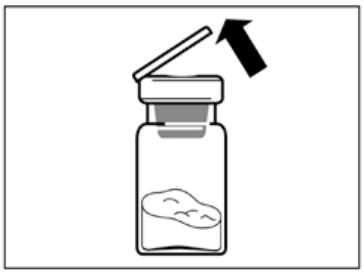
- Remove the Sandostatin LAR injection kit from refrigerated storage.

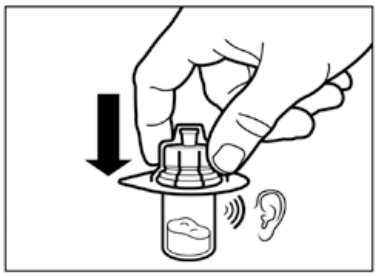
  ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

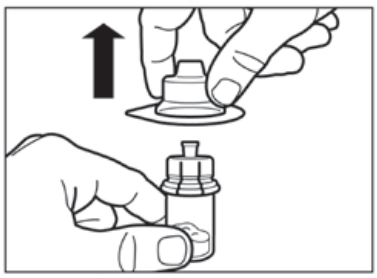
Note: The injection kit can be re-refrigerated if needed.

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 move







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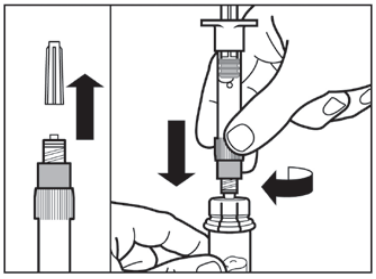
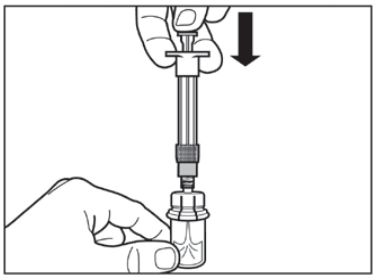
Step 3

- 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.

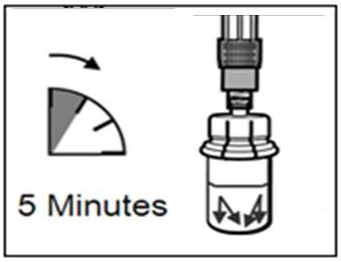




Step 4

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.

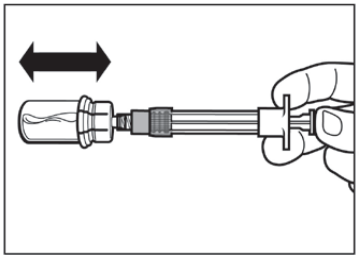


- At this stage prepare the patient for injection.

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.**



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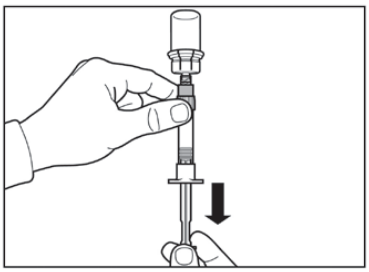
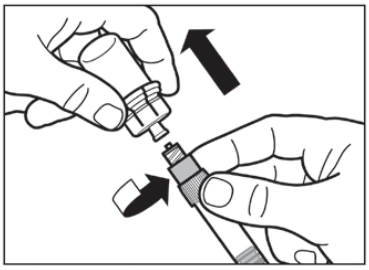
Step 6

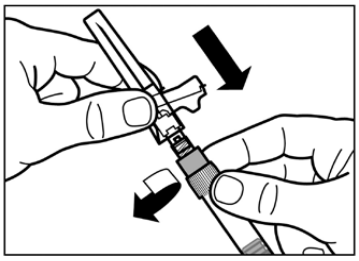
- Turn syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe.
- Unscrew the syringe from the vial adapter.

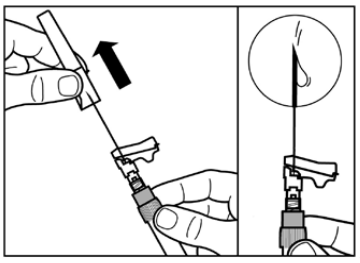




Step 7

- 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.





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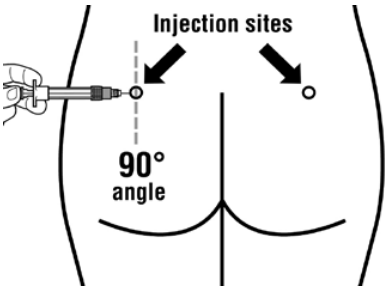
Step 8

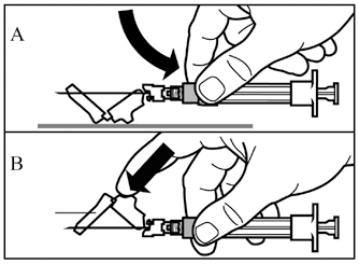
- Sandostatin LAR must be given only by deep intramuscular injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90º angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).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

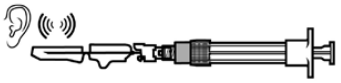


Step 9

- Activate the safety guard over the needle in one of the 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).





בברכה,

לריסה חייקין
רוקחת ממונה

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