NOVARTIS

Sandostatin® LAR®

Composition

Active substance: Octreotide* (as octreotide acetate).

Excipients: Poly(DL-lactide-co-glycolide), mannitol.

Solvents and Processing aids: n-Heptene , Methanol , Methylene Chloride , Nitrogen, Dimeticone (Silicon Oil 350 cSt), Dimeticone (Silicon Oil 1000 cST) , Sorbitan Oleate, Water for injection

Solvent: Carmellose sodium, mannitol, Nitrogen, poloxamer 188 Water for injections.

* rec. INN

Pharmaceutical form and quantity of active substance per unit

Powder and solvent for suspension for injection.

Powder: white to yellowish white powder.

Solvent: clear, colourless to slightly yellow or brown.

Sandostatin LAR is a long-acting depot injection form of octreotide. The powder (microspheres for suspension for injection) is suspended, in the solvent provided, immediately prior to i.m. injection.

Each vial contains:

- *One 10, 20 or 30 mg vial with microspheres for suspension for injection*
- *One pre-filled syringe with solvent: 2.0 ml*
- *An adapter for the vial for reconstitution of the product*
- *A safety needle for injection*

Indications/Potential uses

Acromegaly

Treatment of patients with acromegaly in whom surgery or radiotherapy are inappropriate or ineffective or who are in the latency period before radiotherapy becomes fully effective.

Gastroenteropancreatic (GEP) endocrine tumours

Treatment of patients with signs and symptoms of functional gastroenteropancreatic (GEP) endocrine tumours

- 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, well-differentiated (G1, G2) neuroendocrine tumours of the midgut (small intestine, caecum or appendix).

Dosage/Administration

Sandostatin LAR may only be administered by deep intragluteal injection. Repeat injections should be given alternately in the left and right gluteal muscle.

To ensure correct dosage, the Sandostatin LAR injection kit should be left to stand at room temperature before reconstitution (see "Other information", "Instructions for use and handling" section).

Acromegaly

Treatment should be initiated at a dose of 20 mg Sandostatin LAR every 4 weeks for 3 months. Subsequent dose adjustment should be based on serum growth hormone (GH) and somatomedin C (IGF 1) concentrations and clinical symptoms.

Patients on treatment with s.c. octreotide can start treatment with Sandostatin LAR the day after the last dose of s.c. Sandostatin.

- If, after three months, clinical symptoms and laboratory parameters (GH and IGF-1) are not fully controlled (GH still above 2.5 µg/litre), the dose may be increased to 30 mg every four weeks.
- If GH concentrations are consistently below 1 µg/litre, serum IGF-1 concentrations are normal and most of the reversible signs and symptoms of acromegaly have disappeared after three months of treatment with 20 mg, the dose may be reduced to 10 mg Sandostatin LAR. Serum GH and IGF-1 concentrations and clinical signs and symptoms should be closely monitored in view of the low dosage of Sandostatin LAR.
- In patients consistently receiving the same dose of Sandostatin LAR, GH and IGF-1 concentrations should be determined at six-monthly intervals.

Gastroenteropancreatic endocrine tumours

Functional tumours of the gastroenteropancreatic neuroendocrine system or midgut (carcinoid tumours, VIPomas)

Treatment should be started with 20 mg Sandostatin LAR every four weeks. Patients already receiving treatment with s.c. octreotide should continue at the previously effective dosage for 2 weeks after the first injection of Sandostatin LAR.

In patients in whom symptoms and biological markers have been brought under adequate control after 3 months of treatment, the dose may be reduced to 10 mg Sandostatin LAR every 4 weeks.

In patients in whom it has only been possible to partially control symptoms after three months of treatment, the dose may be increased to 30 mg Sandostatin LAR every four weeks.

During treatment with Sandostatin LAR, there may be some days on which the symptoms associated with GEP tumours are more pronounced. On such days, additional administration of s.c. octreotide, at the dose used prior to Sandostatin LAR therapy, is recommended. This may be necessary during the first two months of treatment, in particular, until therapeutic octreotide levels have been attained.

Neuroendocrine tumours of the midgut

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

Special dosage instructions

Elderly patients

A special dosage is not required for elderly patients at the start of treatment with Sandostatin or Sandostatin LAR.

Children and adolescents

There is no experience of the use of Sandostatin LAR in patients under 18 years old.

Renal impairment

No dose adjustment is required (see "Pharmacokinetics").

Hepatic impairment

The elimination of octreotide may be reduced in patients with liver cirrhosis. In view of the wide therapeutic index of octreotide, dose adjustment is not necessary in cirrhotic patients.

Contraindications

Known hypersensitivity to octreotide or any of the excipients.

Warnings and precautions

General

GH-secreting pituitary tumours may expand, causing serious complications (e.g. restriction of the visual field) and patients must therefore be closely monitored. As soon as evidence of tumour expansion is detected, alternative treatment methods are advisable.

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalisation of insulin-like growth factor 1 (IGF-1) concentrations in female acromegalic patients may possibly restore fertility. Female patients of childbearing potential should be advised to use appropriate contraception during treatment with octreotide (see "Pregnancy/Breast-feeding").

Thyroid function should be monitored in patients receiving long-term treatment with octreotide.

Cardiovascular events

Cases of bradycardia have been reported. Dose adjustment may be necessary for drugs such as beta blockers, calcium channel blockers or other agents used to control the electrolyte and fluid balance.

Gallbladder and gallbladder-related events

The formation of gallstones (cholelithiasis) is very common during treatment with Sandostatin. Gallstones may also occur in conjunction with inflammation of the gallbladder (cholecystitis) and dilatation of the biliary tract (see "Adverse effects"). Gallbladder ultrasonography is recommended before the start of treatment with Sandostatin LAR and at intervals of approx. six months thereafter.

Glucose metabolism

In patients with concomitant insulin-dependent type I diabetes mellitus, Sandostatin LAR may affect glucose regulation and insulin requirements may be reduced. Hypoglycaemia was reported.

S.c. administration of Sandostatin may lead to a postprandial rise in blood sugar in non-diabetics and type II diabetics with partially intact insulin reserves. It is therefore recommended to monitor blood sugar levels accordingly and to adjust anti-diabetic therapy, if required.

Insulinoma patients: Since octreotide is a more potent inhibitor of GH and glucagon secretion than of insulin secretion and because it inhibits insulin secretion more briefly, it may exacerbate and prolong hypoglycaemic episodes. Such patients should be closely monitored.

Nutrition

Octreotide may alter the absorption of dietary fats in some patients.

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

Interactions

Pharmacokinetic interactions

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

Co-administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

A limited amount of published data indicates that somatostatin analogues might reduce the metabolic clearance of substances metabolised by cytochrome P450 enzymes. This is attributed to the suppression of growth hormones. As it cannot be ruled out that octreotide might also have such an effect, caution is indicated when using other drugs that are principally metabolised by CYP3A4 and have a narrow therapeutic index (e.g. quinidine, terfenadine).

Pharmacodynamic interactions

Dose adjustments of medicines such as beta blockers, calcium channel blockers or agents to control fluid and electrolyte balance may be necessary when Sandostatin LAR is co-administered (see "Pharmacokinetics" and precautions"). Dose adjustments of insulin and anti-diabetic medicines may be required when Sandostatin LAR is co-administered (see "Warnings and precautions").

Pregnancy/Breast-feeding

Pregnancy

Animal studies with octreotide have not shown reproductive toxicological effects, apart from transient delayed growth of offspring (see "Preclinical data").

There are no adequate and well-controlled studies in pregnant women. In the post-marketing period, there have been a limited number of reports of women having fetuses or babies with congenital defects and received octreotide, but pregnancy outcomes are unknown in half of these cases. Most of the pregnancies with octreotide during the first trimester of pregnancy at doses ranging from 100 to 300 µg Sandostatin s.c. daily or 20 to 30 mg Sandostatin LAR per month. In approximately two-thirds of the cases of pregnancies with known outcome, the women chose to continue octreotide therapy during their pregnancies. Normal newborns were reported in approximately two-thirds of these pregnancies, but some spontaneous abortions during the first trimester were also reported. Congenital abnormalities or malformations were not observed.

Sandostatin LAR should only be prescribed to pregnant woman if absolutely necessary.

Breast-feeding

It is not known whether octreotide is excreted in human milk. Animal studies have shown excretion of octreotide in the breast milk. Women receiving long-term breast-feed while undergoing treatment with Sandostatin LAR.

Fertility

It is not known whether octreotide has an effect on human fertility. Octreotide did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day (see "Preclinical data").

Effects on the ability to drive and to use machines

No data are available on the effect of Sandostatin LAR on the ability to drive and use machines.

Adverse effects

In clinical studies, the most commonly reported adverse effects following administration of octreotide were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation.

Other commonly reported adverse effects were dizziness, localised pain, biliary sludge, thyroid dysfunction (e.g. decreased TSH, decreased total T4 and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia and hypoglycaemia .

Gastrointestinal disorders and nutrition

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

Faecal fat excretion may increase, but even with long-term octreotide therapy there is no evidence to date that this results in nutritional deficiency due to malabsorption.

Gallbladder and gallbladder-related events

Somatostatin analogues inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or the formation of biliary sludge. Gallstone formation has been reported in 30 % to 50% of patients on long-term s.c. Sandostatin therapy. This value is about 2-5% in the general population (age: 40 to 60 years). Data on long-term Sandostatin LAR therapy in patients with acromegaly or GEP endocrine tumours indicate that, compared with s.c. Sandostatin, treatment with Sandostatin LAR is not associated with a higher incidence of gallstone formation. Gallstones developing during treatment are usually asymptomatic; symptomatic stones should either be treated by dissolution with bile acids or surgically removed.

Pancreatitis

There have been very rare reports of acute pancreatitis. This normally develops within the first hours or days of Sandostatin treatment and resolves following treatment withdrawal. In addition, cholelithiasis-induced pancreatitis has been reported in patients receiving long-term treatment with Sandostatin.

Cardiac disorders

Bradycardia is a common adverse effect of somatostatin analogue treatment such as s.c. octreotide and lanreotide, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression and non-specific ST-T wave changes – have been observed. The relationship of these events to octreotide has not been definitively established because many of the patients in question had underlying heart disease (see "Warnings and Precautions").

Hypersensitivity and anaphylactic reactions

There have been post-marketing reports of hypersensitivity and allergic reactions. These were mainly associated with skin reactions; rarely, the mouth and respiratory tract were affected. Isolated cases of anaphylactic shock have been reported.

Injection site reactions

Injection site reactions reported by patients receiving Sandostatin LAR were pain, redness, haemorrhage, pruritus, swelling or induration. Most of these events did not require any clinical intervention in most cases.

Thrombocytopenia

There have been post-marketing reports of thrombocytopenia, particularly during treatment with Sandostatin (i.v.) in patients with liver cirrhosis and during treatment with Sandostatin LAR. The thrombocytopenia was reversible after discontinuation of treatment.

The above effects observed in clinical studies or in the post-marketing period with octreotide are listed below by MedDRA system organ class and frequency. The frequency is ranked using the following convention: *Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known* (primarily based on spontaneous post-marketing reports; precise frequency cannot be estimated).

Blood and lymphatic system disorders

Not known: Thrombocytopenia

Immune system disorders

Not known: Hypersensitivity reactions (including anaphylactoid reactions).

Endocrine disorders

Common: Hypothyroidism, thyroid dysfunction (e.g. decreased TSH, decreased total T4 and decreased free T4).

Metabolism and nutrition disorders

Very common: Hyperglycaemia (10.8%).

Common: Hypoglycaemia, impaired glucose tolerance, loss of appetite.

Uncommon: Dehydration.

Nervous system disorders

Very common: Headache (12.4%).

Common: Dizziness .

Cardiac disorders

Common: Bradycardia.

Uncommon: Tachycardia.

Not known: Arrhythmias.

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea.

Gastrointestinal disorders

Very common: Diarrhoea (26.1%), abdominal pain (24.2%), nausea (14.3%), flatulence (14.2%), constipation (12.7%).

Common: Dyspepsia, vomiting, abdominal distension, steatorrhoea, discoloured faces.

Not known: Acute pancreatitis.

Hepatobiliary disorders

Very common: Cholelithiasis (12.0%).

Common: Increased transaminases, hyperbilirubinaemia, cholecystitis.

Not known: Increased blood alkaline phosphatase, increased gamma glutamyl transferase, jaundice, cholestasis, cholestatic jaundice, cholestatic hepatitis, acute hepatitis with cholestasis.

Skin and subcutaneous tissue disorders

Common: Pruritus, skin rash, alopecia.

Not known: Urticaria.

General disorders and administration site conditions

Very common: Injection site reactions (10 to 30% depending on the dose and injection interval, e.g. pain, paraesthesia, erythema).

Common: Asthenia.

Overdose

A limited number of accidental overdoses of Sandostatin LAR have been reported. The doses ranged from 100 mg to 163 mg Sandostatin LAR per month. Hot flushes were the only reported adverse effect.

There have been reports of cancer patients receiving doses of up to 60 mg Sandostatin LAR per month and up to 90 mg every 2 weeks. These doses have generally been well tolerated, but the following adverse effects have been reported: frequent urination, fatigue, depression, anxiety, lack of concentration.

The management of Sandostatin LAR overdose is symptomatic.

Properties/Actions

ATC code: H01CB02

Mechanism of action/Pharmacodynamics

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with qualitatively similar pharmacological effects but a considerably longer duration of action. It inhibits pathologically increased secretion of both growth hormone (GH) and of peptides and serotonin produced in the gastroenteropancreatic (GEP) endocrine system.

In animals, Sandostatin is more potent than somatostatin in inhibiting growth hormone (GH), glucagon and insulin release, as well as being more selective for GH and glucagon suppression.

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

- growth hormone release in response to arginine, exercise or insulin-induced hypoglycaemia.
- postprandial release of insulin, glucagon, gastrin and other peptides of the GEP system and the secretion of insulin and glucagon in response to arginine.
- release of thyroid-stimulating hormone (TSH) in response to protirelin (TRH, thyrotropin-releasing hormone).

In contrast to somatostatin, octreotide inhibits GH preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (e.g. GH in acromegalic patients).

Clinical efficacy for different types of tumour

Acromegaly

Sandostatin LAR delivers consistent and therapeutically effective serum octreotide levels, resulting in consistent lowering of GH and normalisation of serum IGF-1. In most patients, Sandostatin LAR produces a marked improvement in clinical manifestations such as headache, sweating, paraesthesia, fatigue, osteoarthralgia and carpal tunnel syndrome. Even if a reduction in tumour size can be expected in some patients during treatment with somatostatin analogues, all patients undergoing such treatment must be regularly monitored (see "Warnings and Precautions").

Treatment with Sandostatin LAR brought about a reduction in tumour volume of over 20% in half of the previously untreated acromegaly patients with GH-secreting pituitary adenoma.

The efficacy and safety of Sandostatin LAR to treat acromegaly was investigated at single doses of 10, 20 or 30 mg in two randomised, double-blind, uncontrolled studies in a total of 93 patients. The primary efficacy parameter was the mean 12-hour GH serum concentrations. The 20 and 30 mg doses of Sandostatin LAR are able to suppress GH levels below 5 µg/litre from day 14 until day 42.

In a subsequent open-label extension study, patients could receive up to 28 further injections (at 28-day intervals) with data on 87 patients available over this treatment period. Dose adjustment between 10 and 30 mg (in exceptional cases up to 40 mg) was possible based on individual response rates. Sandostatin LAR resulted in a sustained suppression of GH levels throughout the dosing interval. These effects were accompanied by a marked reduction in IGF-1 concentrations and a sustained regression of the clinical symptoms of acromegaly.

The tolerability of Sandostatin LAR in these studies was comparable to those of s.c. Sandostatin.

Functional tumours of the gastroenteropancreatic endocrine system

Treatment with Sandostatin LAR provides continuous control of symptoms that are related to the octreotide dose. Octreotide acts on the different types of GEP tumours as follows:

Carcinoid tumours

Use of octreotide may bring about an improvement in symptoms, in particular flush and diarrhoea. In some cases there may also be a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid.

The efficacy and safety of Sandostatin LAR at doses of 10, 20 or 30 mg every four weeks to treat malignant carcinoid syndrome was investigated in a randomised, double-blind study vs Sandostatin s.c. injections. The response rate based on the strength and duration of suppression of carcinoid symptoms is defined as the efficacy endpoint. Treatment success assumes that in each of the 3 months of treatment in the Sandostatin LAR group, emergency treatment with s.c. octreotide is required a maximum of two times over a total of five days. Treatment failure in the Sandostatin s.c. group over the same period is achieved when a dose increase is required a maximum of two times over a total of five days.

The efficacy of Sandostatin LAR was comparable to that of Sandostatin s.c. At the end of the study, 58% of patients on Sandostatin s.c. achieved treatment success, whereas 55%, 50% and 56% of patients achieved treatment success on Sandostatin LAR 10, 20 and 30 mg, respectively.

VIPomas

The principal biochemical feature of these tumours is overproduction of vasoactive intestinal polypeptide (VIP). The condition, which is characterised by severe secretory diarrhoea, is relieved in most cases by treatment with octreotide, with consequent improvement in quality of life. Electrolyte disturbances (e.g. hypokalaemia) associated with this diarrhoea also improve, so that enteral and parenteral fluid and electrolyte replacement can be discontinued. CT scan has indicated slowed growth of tumours, regression or even shrinkage – in some patients, particularly those with liver metastases. Clinical improvement is usually accompanied by reduction – or even normalisation – of plasma VIP-levels.

Glucagonomas

In most cases use of octreotide results in a substantial improvement in the necrolytic migratory rash characteristic of this condition. Octreotide has little effect on the mild form of diabetes mellitus to which glucagonoma patients are prone. There is normally no reduction in the required dosage of insulin or oral antidiabetic agents. Potential diarrhoea responds to therapy, resulting in weight gain. Octreotide frequently brings about an immediate reduction in plasma glucagon. This effect is not sustained as treatment continues, although symptoms continue to improve.

Gastrinomas / Zollinger-Ellison syndrome

Treatment with proton pump inhibitors or H_2-receptor blockers cannot always prevent the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid and does not always alleviate diarrhoea, which may be severe. In most cases, octreotide – either alone or in combination with proton pump inhibitors or H_2-receptor blockers – may reduce increased gastric acid production and induce an improvement in the clinical manifestations (including diarrhoea) in up to 50% of cases. Other manifestations assumed to be due to peptide production by the tumour (e.g. flush) may also respond. Octreotide produces a fall in plasma gastrin levels in some patients.

Insulinomas

Octreotide causes a reduction in circulating immunoreactive insulin. In patients with operable tumours, octreotide may be given pre-operatively to help achieve and maintain normoglycaemia. In some patients with inoperable benign or malignant tumours, octreotide improves regulation of blood sugar, even without a sustained reduction in insulin levels.

GRFomas

This is a rare type of tumour that produces growth-hormone-releasing factor (GRF) alone or in conjunction with other biologically active peptides. Octreotide treatment resulted in improvement of the symptoms of resultant acromegaly in one of the two cases investigated. This effect is probably due to inhibition of GRF and GH secretion. It may be accompanied by a reduction in the size of the enlarged pituitary.

Advanced, well-differentiated neuroendocrine tumours of the midgut

Patients with metastases from well-differentiated functional or non-functional neuroendocrine tumours of the midgut were enrolled in a placebo-controlled study (PROMID). 85 patients were randomised to treatment with Sandostatin LAR 30 mg every 4 weeks (n=42) or placebo (n=43).

The main indicator was time to tumour progression (TTP) based on central radiological review using WHO criteria. Median time to tumour progression was 14.3 months in the Sandostatin LAR group and 5.9 months on placebo (HR = 0.36; 95% CI 0.21 to 0.61; p=0.0001).

Treatment effect was similar in patients with functional (HR = 0.41; 95% CI 0.18 to 0.92) and non-functional tumours (HR = 0.32; 95% CI 0.15 to 0.66).

As the pooled interim analysis at 18 months showed a significant clinical benefit for Sandostatin LAR, patient recruitment was stopped. The Sandostatin LAR arm was able to continue treatment until progression, while the placebo arm was switched to active treatment.

Overall survival was evaluated after an additional follow-up of 4.5 years. No difference was found between the two study arms.

Pharmacokinetics

The pharmacokinetic profile of octreotide following 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. Following a single i.m. injection of Sandostatin LAR, the serum octreotide concentration reaches a transient initial peak within one hour of administration, followed by a gradual decrease to a low octreotide level below the detection limit within 24 hours.

Less than 0.5% of the initial dose release occurs on day one. Octreotide remains at subtherapeutic levels for the next 7 days after injection of Sandostatin LAR in the majority of patients.

Octreotide levels reach a plateau around day 14, at which they remain relatively constant during the following 3 to 4 weeks.

After about day 42, the octreotide concentration begins to decrease slowly again due to the terminal degradation of the polymer matrix.

Distribution

The volume of distribution is 0.27 litres/kg and the total body clearance is 160 ml/minute. Plasma protein binding is 65%. The amount of octreotide bound to blood cells is very small.

Elimination

The elimination half-life after subcutaneous administration is 100 minutes. Most of the peptide is excreted in the faeces, while some 32% is excreted unchanged in the urine.

Pharmacokinetics in special patient populations

Renal impairment: Renal impairment did not affect total exposure (AUC) to subcutaneously administered octreotide.

Hepatic impairment: Liver cirrhosis, but not fatty liver disease, reduces the elimination of octreotide (by 30%).

Preclinical data

Mutagenicity

Octreotide for s.c. administration and/or its metabolites showed no mutagenic potential when investigated in vitro in validated bacterial and mammalian cell strains. In one study, an increased frequency of chromosomal changes were observed in V79 Chinese hamster cells, albeit at high and cytotoxic concentrations only. However, the frequency of chromosomal aberrations was not elevated in human lymphocytes that had been incubated with octreotide acetate. In vivo, no clastogenic activity was observed in the bone marrow of mice treated with octreotide (micronucleus test) and no evidence of genotoxicity was found for male mice in a DNA repair assay on sperm heads. The microspheres also showed no mutagenic potential in the standard genotoxicity assays.

Carcinogenicity/Chronic toxicity

Long-term studies in rats, mice and dogs did not reveal any potential for chronic toxicity.

In a carcinogenicity study, octreotide was administered s.c. to rats for 116 weeks. The incidence of reported endometrial adenocarcinomas was statistically significant at the highest s.c. dose of 1.25 mg/kg per day and was evidently associated with a disturbed hormonal balance. The available data show that these endocrine-mediated tumours are species-specific in rats and therefore not relevant for humans.

Reproductive toxicity

Reproductive and development toxicity studies have been performed in rats and rabbits at doses of up to 1 mg/kg body weight per day. Octreotide did not impair fertility in male and female rats. There was no evidence of teratogenic, embryofetal or other reproduction effects due to octreotide. Some delay in the physiological growth was noted in the offspring of rats which was transient and most likely attributable to GH inhibition brought about by excessive pharmacodynamic activity. In pre- and post-natal development studies, late testicular descent was observed in male offspring of maternal animals treated during pregnancy and lactation. However, the fertility of the F1 offspring was normal. It is assumed that these observations concerning inhibited growth are caused by octreotide.

The microspheres did not have any reproductive toxicological effects when tested in standard studies for reproductive toxicity in rats and rabbits.

Other information

Incompatibilities

Sandostatin LAR microspheres for injection may only be used for the preparation of a single dose and must not be diluted or mixed with other substances. For this reason, no data on compatibility with other solutions or substances have been collected.

Shelf-life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

For prolonged storage, Sandostatin LAR vials should be kept in a refrigerator at 2 to 8°C. Do not freeze.

Protect from light. Do not store Sandostatin LAR above 25°C in the 24 hours prior to injection. The suspension must not be prepared until immediately before injection. Keep out of the reach of children.

Instructions for use and handling

Instructions for i.m. injection of Sandostatin® LAR®

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

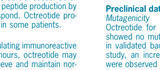
Sandostatin LAR may only be administered by deep intragluteal injection and **never** by the i.v. route.

Carefully follow the instructions below to ensure complete wetting and uniform suspension of the powder prior to injection.

The suspension must not be prepared until immediately before injection.

Repeat injections should be given alternately in the left and right gluteal muscles.

Pack contents:



a Vial with Sandostatin LAR dry powder
b Injection kit with solvent
c Adapter for the vial
d Safety needle
Reconstitution must be carried out under aseptic conditions.

Step 1

Take Sandostatin LAR injection kit out of the refrigerator and allow it to reach room temperature. Leave the kit to stand at room temperature for **at least 30 to 60 minutes**, but no longer than 24 hours.

Step 2

Remove the cap from the vial containing Sandostatin LAR.

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

Then remove lid film of the vial adapter from the blister pack. Do not remove the adapter from the blister pack. Using the blister pack, position the adapter on top of the vial. Push it down until you hear an audible click. Once the adapter has clicked into place, lift the blister pack off with a vertical movement and dispose of it.

Step 3

Remove the cap from the pre-filled syringe containing the solvent and screw the syringe on to the vial adapter.

Slowly push the plunger down and inject all of the solvent into the vial without disturbing the Sandostatin LAR powder.

Step 4

Let the vial stand for 5 minutes until the solvent has completely wetted the Sandostatin LAR powder. The patient should be prepared in the meantime. Without inverting the vial, check the powder on the bottom and inside surface of the vial. If there are still dry spots, allow the vial to remain standing so that complete wetting can be achieved.

Note: It is normal for the plunger to move up as there might be some slight overpressure in the vial.

Step 5

Once the dry powder is completely wetted, push the plunger all the way down in the pre-filled syringe.

Hold the plunger down and gently turn the vial horizontally for at least 30 seconds. Check whether the powder on the bottom and on the inside surface of the vial has completely dissolved (a uniform milky solution should be obtained). If this is not the case, the vial should be gently turned horizontally for another 30 seconds, approximately.

IMPORTANT NOTE: The vial must not be vigorously shaken since this may cause the suspension to flocculate and thus become unusable.

Step 6

Disinfect the injection site with an alcohol swab.

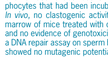
Turn the pre-filled syringe and vial upside down and slowly pull the plunger back so that all of the contents of the vial are drawn into the pre-filled syringe.

Unscrew the pre-filled syringe from the adapter straight away.

Step 7

Screw the safety needle onto the syringe.

Carefully turn the pre-filled syringe in order to obtain a uniform, milky suspension.

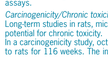


Remove the needle cap.

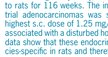
Gently tap the pre-filled syringe in order to remove any visible air bubbles. Check the injection site for any contamination.

Proceed **immediately** to step 8.

Step 8



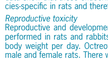
Insert the needle into the right or left gluteal muscle at a 90° angle to the skin and draw back the plunger in order to ensure that no blood vessel has been penetrated. Otherwise the position of the needle should be changed.



Applying steady pressure, inject slowly i.m. by deep intragluteal injection until the syringe is empty.

After performing the injection, activate the needle safety guard as shown in step 9.

Step 9



Using a single-handed operation, activate the needle safety guard:

A) either by pressing down the hinge of the safety guard on a hard surface (figure A)

B) or by pushing the hinge forward with your finger. (figure B)

An audible "click" confirms proper activation of the safety guard.

Dispose of the adapter and the pre-filled syringe in a sharps container or a secure waste bin immediately.

Pack sizes

10 mg Sandostatin LAR vial: 1 Glass vial of 10mg + 1 prefilled syringe of 2 ml + 1 Vial Adaptor + 1 needle
20 mg Sandostatin LAR vial: 1 Glass vial of 20mg + 1 prefilled syringe of 2 ml + 1 Vial Adaptor + 1 needle
30 mg Sandostatin LAR vial: 1 Glass vial of 30mg + 1 prefilled syringe of 2ml + 1 Vial Adaptor + 1 needle

Not all Pack sizes are marketed

Manufactured by
Sandoz GmbH, Schaftenau, Austria for Novartis Pharma AG, Basle, Switzerland

Batch Releaser
Novartis Pharma Stein AG, Switzerland

Information last revised
December 2017
® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- *A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.*
- *Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.*
- *The doctor and the pharmacist are experts in medicine, its benefits and risks.*
- *Do not by yourself interrupt the period of treatment prescribed for you.*
- *Do not repeat the same prescription without consulting your doctor.*

Keep medicaments out of reach of children

Council of Arab Health Ministers Union of Arab Pharmacists