Sandostatin® LAR®

1. NAME OF THE MEDICINAL PRODUCT
Sandostatin® LAR®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial containing: Microspheres for suspension for injection
Active: Octreotide* free peptide, 10, 20 or 30 mg nominally 4.15 % of fill weight equivalent to 4.65 % of octreotide acetate
Other: Poly (DL-lactide-co-glycolide); sterile mannitol
One prefilled syringe with 2.5 ml of solvent
Solvent: sodium carboxymethylcellulose; mannitol; water to give an isotonic solution
Two needles (1.1 x 40 mm)
* INN. rec.

3. PHARMACEUTICAL FORM
Powder and solvent for suspension for injection.
Powder: white to off-white powder.
Solvent for suspension for injection: clear, colourless solution.
Sandostatin® LAR® is a long-acting depot injection form of octreotide. Powder (microspheres for suspension for injection) to be suspended in a vehicle immediately prior to i.m. injection.
Sandostatin LAR suspension contains less than 1 mmol (23 mg) of sodium per dose, i.e. essentially ‘sodium-free’.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of patients with acromegaly
- Who are adequately controlled on s.c. treatment with Sandostatin
- In whom surgery, radiotherapy or dopamine agonist treatment is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see posology and method of administration)

Relief of symptoms associated with gastro entero pancreatic endocrine tumours:
- Carcinoid tumours with features of the carcinoid syndrome
- VIPomas
- Glucagonomas
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 Instructions for use/handling).

Acromegaly
For patients who are adequately controlled with s.c. Sandostatin, it is recommended to start treatment with the administration of 20 mg Sandostatin LAR at 4-week intervals for 3 months. Treatment with Sandostatin LAR can be started on 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 2.5μg/L), the dose may be increased to 30 mg every 4 weeks.

For patients whose GH concentrations are consistently below 1 μg/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. In order to permit successful endocrine testing of the completeness of tumour removal 5-6 weeks post surgery, the last injection of Sandostatin LAR should be administered at least 3-4 weeks prior to surgery.

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

For patients in whom surgery, radiotherapy or dopamine agonist treatment 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.

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. Response should be assessed after 3 months of treatment.

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.

Dose titration:
For patients in whom symptoms and biological markers are well controlled after three months of treatment, the dose may be reduced to 10 mg Sandostatin LAR every 4 weeks.

For patients in whom symptoms are only partially controlled after 3 months of treatment, the dose may be increased to 30 mg Sandostatin every 4 weeks.
For days when symptoms associated with gastro-entero-pancreatic tumours may increase during treatment with Sandostatin LAR, additional administration of s.c. Sandostatin is recommended at the dose used prior to the Sandostatin LAR treatment. This may occur mainly in the first 2 months of treatment until therapeutic concentrations of octreotide are reached.

**Use in patients with impaired renal function**

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

**Use in patients with impaired hepatic function**

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

**Use in elderly patients**

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

**Use in children**

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

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

**General**

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

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

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

**Cardiovascular related events**

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

**Gallbladder and related events**

Development of gallstones has been reported in 15 to 30\% of long-term recipients of s.c. Sandostatin. The prevalence in the general population (aged 40 to 60 years) is about 5 to 20\%. 

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Long-term exposure to Sandostatin LAR of patients with acromegaly or gastro-entero-pancreatic tumours suggests that treatment with Sandostatin LAR does not increase the incidence of gallstone formation, compared with s.c. treatment. Ultrasonic examination of the gallbladder before and at about 6 monthly intervals during Sandostatin LAR therapy is however recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery. (See page 16 'Recommendation for the management of patients during Sandostatin LAR treatment with respect to the development of gallstones'). [This section to be included ONLY as an advice, NOT COMPULSORY to include (depending on s.c. Sandostatin registration).]

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

In patients with concomitant Type I diabetes mellitus, Sandostatin LAR is likely to affect glucose regulation, and insulin requirements may be reduced. 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 Pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience, data on a limited number of exposed pregnancies have been reported in patients with acromegaly, however, in half of the cases the pregnancy outcomes are unknown. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from
100 to 300 micrograms/day of Sandostatin s.c. or 20 to 30 mg/month of Sandostatin LAR. In approximately two-thirds of the cases with known outcome, the women elected to continue octreotide therapy during their pregnancies. In most of the cases with known outcome, normal newborns were reported but also several spontaneous abortions during the first trimester, and a few induced abortions.

There were no cases of congenital anomalies or malformations due to octreotide usage in the cases that reported pregnancy outcomes.

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

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

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent adverse reactions reported during octreotide therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with octreotide administration were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness, localized pain, biliary sludge, thyroid dysfunction (e.g., decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycaemia.

Intermittent gastrointestinal side effects resembling acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding can occur in about 10% of patients, but usually decline with continued treatment.

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

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

In very rare instances, acute pancreatitis has been reported within the first hours or days of Sandostatin s.c. treatment and resolved on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term Sandostatin s.c. treatment.

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 Special warnings and precautions for use).

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

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Very common: Diarrhoea, crampy abdominal pain, nausea, constipation, flatulence. Common: Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td>Common: Hypothyroidism, thyroid dysfunction (e.g., decreased TSH, decreased Total T4, and decreased Free T4).</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Very common: Injection site localized pain, swelling and irritation.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common: Elevated transaminase levels.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: Pruritus, rash, alopecia.</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>Common: Dyspnoea.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Immune disorders</th>
<th>Anaphylaxis, allergy/hypersensitivity reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, irritation, rash</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Gallstones, acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmias.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels.</td>
</tr>
</tbody>
</table>

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: anti-growth hormone, 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 gastro-entero-pancreatic (GEP) endocrine system.

In animals, octreotide is a more potent inhibitor of GH, glucagon and insulin release than somatostatin, with greater selectivity for GH and glucagon suppression.

In healthy subjects octreotide, like somatostatin, has been shown to inhibit
- release of GH stimulated by arginine, exercise and insulin-induced hypoglycaemia,
- post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP system, and arginine-stimulated release of insulin and,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH)

Unlike somatostatin, octreotide inhibits GH preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. GH in patients with acromegaly).

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 tumor volume reduction of > 20% in a significant proportion (50%) of patients.

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

Glucagonomas:
Administration of octreotide results in most cases in substantial improvement of the necrotic migratory rash which is characteristic of the condition. The effect of 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 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.

5.2 Pharmacokinetics 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 allow undetectable octreotide level within 24 hours. After this 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, reach plateau concentrations at around day 14 and remain relatively constant 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 patient with acromegaly, mean plateau octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg of sandostatin LAR amount to 358 ng/L, 926 ng/L and 1710 ng/L.
respectively. Steady-state serum octreotide concentrations, reached after 3 injections at 4-week intervals, are higher by a factor of approximately 1.6 to 1.8 and amount to 1557 ng/L and 2384 ng/L after multiple injections of 20 mg and 30 mg of Sandostatin LAR, respectively.

In patients with carcinoid tumours, the mean (and median) steady state concentrations of octreotide after multiple injections of 10 mg, 20 mg, 30 mg of Sandostatin LAR given at 4-week intervals also increased linearly with dose and were 1231 (894) ng/ L, 2620 (2270) ng/L, and 3928 (3010) 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.

5.3 Preclinical safety data

Acute toxicity

Acute toxicity studies of octreotide in mice revealed LD₃₀ values of 72 mg/kg by the i.v. route and of 470 mg/kg by the s.c.route. The acute i.v. LD₃₀ value of octreotide in rats was determined at 18 mg/kg. Octreotide acetate was well tolerated by dogs receiving up to 1 mg/kg body weight by i.v. bolus injection.

Repeated dose toxicity

In repeated dose study performed in rats by i.m. injection of 2.5 mg Sandostatin LAR in 50-mg microspheres every 4 weeks for 21 weeks, with necropsy at 26 weeks, no drug-related necropsy findings were observed. The only histopathological findings considered to be of significance were at the injection site in treated and control animals, where the microspheres had provoked a reversible granulomatous myositis. After single i.m. injection of Sandostatin LAR in rats and rabbits, biodegradation of microspheres was complete by a day 75 after injection in both species.

Mutagenicity

Sandostatin administered s.c. and or its metabolites were devoid of mutagenic potential when investigated in vitro in validated bacterial and mammalian cell test systems. Increased frequencies of chromosomal changes were observed in V79 Chinese hamster cells in vitro, albeit at high and cytotoxic concentrations only. Chromosomal aberrations were however not increased in human lymphocytes incubated with octreotide acetate in vitro. In vivo, no clastogenic activity was observed in the bone marrow of mice treated with octreotide i.v. (micronucleus test) and no evidence of genotoxicity was obtained in male mice using a DNA repair assay on sperm heads. The microspheres were devoid of mutagenic potential when tested in a validated in vitro bacterial assay.

Carcinogenicity/chronic toxicity

In studies in rats in which s.c. Sandostatin at daily doses up to 1.25 mg/kg body weight were administered, fibrosarcomas were observed, predominantly in a number of male animals, at the
s.c. injections site after 52, 104 and 113/116 weeks. Local tumours accured also in the control rats, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were observed neither in mice receiving daily s.c. injections of Sandostatin at doses up to 2 mg/kg for 98 weeks, nor in dogs which were treated with daily s.c. doses of the drug for 52 weeks.

The 116-week carcinogenicity study in rats with s.c. Sandostatin also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest s.c. dose level of 1.25 mg/kg per day. The findings was associated with an increased incidence of endometritis, a decreased number of ovarian corpora lutea, a reduction in mammary adenomas and the presence of uterine glandular and luminal dilation, suggesting a state of hormonal imbalance. The available information clearly indicates that the findings of endocrine-mediated tumours in rats are species-specific and are not relevant for the use of the drugs in humans.

Reproduction toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vial
Poly (DL-lactide-co-glycolide); mannitol

Solvent
Sodium carboxymethylcellulose; mannitol; water for injection

6.2 Incompatibilities

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

6.3 Special precautions for storage

Store at 2 °C to 8°C, protect from light. Sandostatin LAR can remain at room temperature on the day of injection. Do not store Sandostatin LAR above 25°C during a period of approx. 24 prior to injection. The suspension, however, must not be prepared until immediately before injection. Sandostatin LAR should be kept out of the reach of children.

6.4 Nature and content of container

The microspheres are packaged in 5-mL glass vials, with a Teflon-faced rubber stopper and sealed with an aluminium flip-off seal. The vehicle is packaged in the prefilled syringe, and contain of 2.5 ml of solvent.
Special precautions for disposal

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

6.5 Instruction for use/handling

Instruction for intramuscular injection of Sandostatin LAR

See attached pages

HARUS DENGAN RESEP DOKTER

PACKAGE QUANTITIES AND REGISTRATION NUMBER

Pack Sizes:
Box, 1 Vial @ 5 ml + Prefilled Syringe @ 2.5 ml Solvent + Two Sterile Needles

Sandostatin® LAR® 10 mg Reg. No. DKI0567505144A1
Sandostatin® LAR® 20 mg Reg. No. DKI0567505144B1
Sandostatin® LAR® 30 mg Reg. No. DKI0567505144C1

Manufactured by Sandoz GmbH, Langkampfen, Austria (Plant Schaftenau) for Novartis Pharma AG, Basel, Switzerland.
Imported by PT Novartis Indonesia, Jakarta, Indonesia.

RENEWAL

Last updated based on BPT 30.11.07
Instructions for intramuscular injection of Sandostatin® LAR®
For deep intragluteal injection only.
The suspension must not be prepared until immediately before injection
Contents:

| One vial containing powder | One syringe containing solvent + two needles |

Carefully follow the instructions below to ensure complete wetting and uniform suspension of the powder prior to injection.
Sandostatin LAR should only be administered by a trained health professional.

<table>
<thead>
<tr>
<th><img src="image1.png" alt="Image" /></th>
<th><img src="image2.png" alt="Image" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allow the Sandostatin LAR vial and the prefilled syringe containing the solvent to reach room temperature. Remove the cap from the vial containing Sandostatin LAR. Tap the vial lightly to ensure that the powder settles at the bottom of the vial. Remove the cap from the prefilled syringe containing the solvent. Attach one of the supplied needles to the syringe.</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><img src="image3.png" alt="Image" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disinfect the rubber stopper of the vial with an alcohol swab. Insert the needle through the centre of the rubber stopper of the Sandostatin LAR vial.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><img src="image4.png" alt="Image" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Without disturbing the Sandostatin LAR powder, carefully inject all of the solvent into the vial, allowing the solvent to run down the inside surface of the vial. The solvent must not be injected directly into the powder. Withdraw the needle from the rubber stopper.</td>
</tr>
</tbody>
</table>
Do not disturb the vial until the solvent has completely wetted the Sandostatin LAR powder (at least 2-3 minutes).

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.

Once complete wetting has occurred, gently swirl the vial for 30-60 seconds until a uniform milky suspension is obtained. **Vigorous shaking of the vial is not allowed** because otherwise the suspension might flocculate, and thus become unusable.

Immediately reinsert the needle through the rubber stopper and then, pointing the tip of the needle down and keeping the vial tilted at an approximately 45° angle, slowly draw the entire contents of the vial into the syringe. Do not invert the vial when filling the syringe because doing so might affect the amount withdrawn.

It is normal for a small amount of suspension to remain on the inside surface and bottom of the vial. This has been taken into account as a calculated overfill.

Change the needle immediately (supplied in pack).

The suspension must be administered as soon as it has been prepared. If necessary, gently invert the syringe to maintain a uniform suspension.

Expel the air from the syringe.

Disinfect the injection site with an alcohol swab. Insert the needle into the left or right gluteal muscle and draw back the plunger in order to ensure that no blood vessel has been penetrated. Applying steady pressure, inject slowly i.m. by deep intragluteal injection. If the needle becomes blocked, replace it with a new needle of the same size (1.1 mm × 40 mm).

Sandostatin LAR may only be administered by deep intragluteal injection, and never via the intravenous route. Select an alternative site if a blood vessel has been penetrated. Repeat injections should be given alternately in the left and right gluteal muscles.