SCHEDULING STATUS: **S4**

PROPRIETARY NAMES AND DOSAGE FORMS

SANDOSTATIN® Ampoule 0,05 mg per 1 ml

SANDOSTATIN® Ampoule 0,1 mg per 1 ml

SANDOSTATIN® Vial 1 mg per 5 ml

COMPOSITION

SANDOSTATIN Ampoule 0,05 mg per 1 ml: Each 1 ml of solution contains 0,05 mg octreotide.

SANDOSTATIN Ampoule 0,1 mg per 1 ml: Each 1 ml of solution contains 0,1 mg octreotide.

SANDOSTATIN Vial 1 mg per 5 ml: Each 1 ml of the multidose solution contains 0,2 mg octreotide (1 mg per 5 ml).

As preservative: Phenol 0,05 % m/v.

SANDOSTATIN solution for injection contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially 'sodium-free'.

List of excipients:

Ampoules:

Lactic acid, mannitol, sodium hydrogen carbonate, water for injections.

Multidose vials:

Lactic acid, phenol, mannitol, sodium hydrogen carbonate, water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 34. Other

PHARMACOLOGICAL ACTION

Octreotide is a synthetic octapeptide analogue 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-enteropancreatic (GEP) endocrine system.

In normal healthy subjects octreotide has been shown to inhibit:

Release of growth hormone (GH) stimulated 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).

Pharmacokinetics:

After subcutaneous injection octreotide is rapidly and completely absorbed. Peak plasma concentrations are reached within 30 minutes. The elimination after subcutaneous administration takes place with a half-life of 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes, respectively. Most of the peptide is eliminated via the faeces, while approximately 32 % is excreted unchanged into the urine. The volume of distribution is 0,27 L/kg and the total body clearance 160 ml/minute. Plasma protein binding amounts to 65 %. The amount of octreotide bound to blood cells is negligible.

Impaired renal function did not affect the total exposure (AUC) to octreotide administered as subcutaneous injection.

The elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease.

INDICATIONS

Symptomatic control and reduction of growth hormone (GH) and IGF-1 plasma levels in patients with acromegaly who are inadequately controlled by surgery or radiotherapy. SANDOSTATIN treatment is also indicated for acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.

Relief of symptoms associated with functional gastro-enteropancreatic endocrine tumours associated with:

- Carcinoid tumours with features of the carcinoid syndrome.
- VIPomas.

SANDOSTATIN is not an antitumour therapy and is not curative in these patients.

Emergency management to stop bleeding and to protect from re-bleeding due to gastro-oesophageal varices in patients with cirrhosis. SANDOSTATIN is to be used in association with specific treatment such as endoscopic sclerotherapy.

CONTRAINDICATIONS

Known hypersensitivity to octreotide or to any of the excipients.

WARNINGS AND SPECIAL PRECAUTIONS

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 deprivation.

Gastro-Entero Pancreatic (GEP) endocrine tumours:

In the treatment of gastro-entero pancreatic endocrine tumours, sudden escape from symptomatic control by SANDOSTATIN may occur infrequently, with rapid recurrence of severe symptoms.

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 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 SANDOSTATIN (see Pregnancy and Lactation).

Thyroid function should be monitored in patients receiving prolonged treatment with SANDOSTATIN. There is a progressive drop in thyroxine levels.

Cardiovascular related events:

Cases of bradycardia have been reported (frequency: common). Dose adjustments of medicines such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary.

Glucose metabolism:

Because of its inhibitory action on growth hormone, glucagon, and insulin, SANDOSTATIN may affect glucose regulation. Post-prandial glucose tolerance may be impaired and, in some instances, the state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

Insulin requirements of patients with type I diabetes mellitus therapy may be reduced by administration of SANDOSTATIN. In non-diabetics and type II diabetics with partially intact insulin reserves, SANDOSTATIN administration can result in prandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

Oesophageal varices:

Since there is an increased risk, following bleeding episodes from oesophageal varices, for the development of insulin-dependent diabetes or for changes in insulin requirement in patients with pre-existing diabetes, an appropriate monitoring of blood glucose levels is mandatory.

Gallbladder and related events:

Cholelithiasis is a very common event during Sandostatin treatment and may be associated with cholecystitis and biliary dilation (see Side Effects). Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during SANDOSTATIN therapy is therefore recommended.

Nutrition:

SANDOSTATIN 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 SANDOSTATIN therapy. Monitoring of vitamin B12 1evels is recommended during therapy with SANDOSTATIN in patients who have a history of vitamin B12.

INTERACTIONS

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 is administered concomitantly (see Warnings and Special precautions).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin is administered concomitantly (see Warnings and Special precautions).

SANDOSTATIN has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Concomitant administration of SANDOSTATIN and bromocriptine increases the availability of bromocriptine and reduces both GH and IGF-1 levels more effectively than with either medicine alone.

Limited published data indicate that somatostatin analogs 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 SANDOSTATIN may have this effect, other medicines mainly metabolized by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g. quinidine).

PREGNANCY AND LACTATION

Pregnancy

Experience with SANDOSTATIN in pregnant or breast feeding women is limited. Safety in pregnancy has not been established.

Lactation

Patients should not breast-feed during SANDOSTATIN treatment.

DOSAGE AND DIRECTIONS FOR USE

Acromegaly:

Initially 0,05 mg to 0,1 mg by subcutaneous injection every 8 or 12 hours. Dosage adjustment should be based on monthly assessment of the effects on the level of circulating GH and IGF-1 levels (target: GH < 2,5 ng/ml; IGF-1 within normal range) and clinical symptoms as well as on tolerability. In most patients the optimal daily dose will be 0,3 mg. A maximum dose of 1,5 mg per day should not be exceeded.
For patients on a stable dose of SANDOSTATIN, assessment of IGF-1 and/or GH should be made every 6 months.

Gastro-entero pancreatic endocrine tumours:

Initially 0,05 mg once or twice daily by subcutaneous injection. Depending on clinical response, effect on levels of circulating tumour produced hormones, (in cases of carcinoid tumours, on the urinary excretion of 5-hydroxyindole acetic acid) and on tolerability, dosage can be gradually increased to 0,1 to 0,2 mg three times daily. Under exceptional circumstances higher doses may be required. Maintenance doses have to be adjusted individually.

In carcinoid tumours, if there is no beneficial response within 1 week of treatment with SANDOSTATIN at the maximum tolerated dose, therapy should not be continued.

Bleeding gastro-oesophageal varices:

25 micrograms/hour by continuous intravenous infusion for 5 days. SANDOSTATIN can be used in dilution with 0,9% sodium chloride solution.

In elderly patients treated with SANDOSTATIN, there was no evidence for reduced tolerability or altered dosage requirements.

Experience with SANDOSTATIN in children is limited.

In patients with liver cirrhosis, the half-life of SANDOSTATIN may be increased, necessitating adjustment of the maintenance dosage.

Impaired renal function did not affect the total exposure (AUC) to SANDOSTATIN administered as subcutaneous injection; therefore no dose adjustment of SANDOSTATIN is necessary.

Note:

Subcutaneous injection:

To reduce local discomfort it is recommended that the solution reach room temperature before injection. Multiple injections at short intervals at the same site should be avoided. Ampoules should be opened just prior to administration, and any unused portion discarded. To prevent contamination it is recommended to puncture the cap of the multidose vial not more than 10 times.

Intravenous infusion:

SANDOSTATIN should be inspected visually for discolouration and particulate matter prior to administration.

SANDOSTATIN (octreotide acetate) is physically and chemically stable for 24 hours in sterile 0,9% sodium chloride solutions or sterile solutions of dextrose (glucose) 5 % in water. However, because SANDOSTATIN can affect glucose homeostasis, it is recommended that physiological saline solutions be used rather than dextrose. The diluted solutions are physically and chemically stable for at least 24 hours below 25 °C. From a microbiological point of view, the diluted solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the user

and should be at 2 °C to 8 °C. Before administration the solution has to be brought to room temperature again.

The cumulated time between reconstitution, dilution with infusion media, storage in a refrigerator, and end of administration must not be longer than 24 hours.

In cases where SANDOSTATIN is to be administered by intravenous infusion, the contents of one 0,5 mg ampoule should normally be dissolved in 60 ml 0,9% sodium chloride, and the resulting solution should be infused by means of an infusion pump. This should be repeated as often as necessary until the prescribed duration of treatment is reached. SANDOSTATIN has also been infused in lower concentrations.

Incompatibilities:

SANDOSTATIN is not stable in Total Parenteral Nutrition (TPN) solutions.

SIDE EFFECTS

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

The most commonly reported adverse reactions in clinical trials with SANDOSTATIN 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.

The following adverse drug reactions have been accumulated from clinical studies with SANDOSTATIN:

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, <1/1000), 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

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).
Cardiac disorders: Common: Bradycardia Uncommon: Tachycardia.
Respiratory, thoracic and mediastinal disorders: Common: Dyspnoea
Gastrointestinal disorders:

Very Common: Diarrhoea, abdominal pain, nausea, constipation, flatulence. Common: Dyspepsia, vomiting, abdominal distension, steatorrhoea, loose stools, discolouration of faeces.
Hepato-biliary disorders: Very common: Cholelithiasis Common: Cholecystitis, biliary sludge, hyperbilirubinaemia.
Metabolism and nutrition disorders: Very common: Hyperglycaemia Common: Hypoglycaemia, impaired glucose tolerance, anorexia decreased appetite Uncommon: Dehydration
Skin and subcutaneous tissue disorders: Common: Pruritus, rash, alopecia.
General disorders and administration site conditions: Very Common: Injection site reaction. Common: Asthenia
Investigations: Common: Elevated transaminase levels.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions reported in Table 2 have been derived from post-marketing experience with Sandostatin LAR via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions derived from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders: Thrombocytopenia
Immune system disorders: Anaphylactic reaction, 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: Dysrhythmias
Investigations: Increased blood alkaline phosphatase levels, increased gamma glutamyl transferase levels.

Description of selected side effects

Gastrointestinal disorders and nutrition

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 SANDOSTATIN has led to nutritional deficiency due to malabsorption.

Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of SANDOSTATIN s.c. administration that is, by injecting between meals or on retiring to bed.

Gallbladder and related reactions

Somastatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. The incidence of gallstone formation with SANDOSTATIN treatment is estimated to be between 15 to 30 %. The incidence in the general population is 5 to 20 %. The presence of gallstones or biliary sludge in SANOSTATIN-treated patients is largely asymptomatic. Symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Injection site reactions

Pain or a sensation of stinging, tingling or burning at the site of subcutaneous (s.c.) injection, with redness and swelling, rarely lasting more than 15 minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection, or by injecting a smaller volume using a more concentrated solution.

Cardiac disorders

Bradycardia is a common side effect with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, EGG 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 SANDOSTATIN is not established because many of these patients have underlying cardiac diseases (see Warnings and Special Precautions).

Pancreatitis

Acute pancreatitis has been reported within the first hours or days of SANDOSTATIN s.c. treatment and resolved on withdrawal of SANDOSTATIN. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term SANDOSTATIN s.c. treatment.

Thrombocytopenia

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No life-threatening reactions have been reported after acute overdosage; the maximum single dose so far given to an adult has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within twenty-four hours of administration of SANDOSTATIN.

A limited number of accidental overdoses of SANDOSTATIN in adults and children have been reported. In adults, the doses ranged from 2,400- 6,000 micrograms/day administered by continuous infusion (100- 250 micrograms/hour) or subcutaneously (1,500 micrograms three times a day). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis. In children, the doses ranged from 50 - 3,000 micrograms/day administered by continuous infusion (2.1 - 500 micrograms/hour) or subcutaneously (50 - 100 micrograms). The only adverse event reported was mild hyperglycaemia. No unexpected adverse events have been reported in cancer patients receiving SANDOSTATIN at doses of 3,000- 30,000 micrograms/day in divided doses subcutaneously.

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 and supportive.

IDENTIFICATION

SANDOSTATIN Ampoule 0,05 mg per 1 ml:

A clear, colourless solution in a 1 ml ampoule of uncoloured glass, colour coded with a blue ring and a yellow ring on the neck of the ampoule.

SANDOSTATIN Ampoule 0,1 mg per 1 ml:

A clear, colourless solution in a 1 ml ampoule of uncoloured glass, colour coded with a blue ring and a green ring on the neck of the ampoule.

SANDOSTATIN Vial 1 mg per 5 ml:

A clear, colourless solution in a vial of uncoloured glass with rubber stopper.

PRESENTATION:

SANDOSTATIN Ampoule 0,05 mg per 1 ml: Carton of 5 ampoules of 1 ml each.

SANDOSTATIN Ampoule 0,1 mg per 1 ml: Carton of 5 ampoules of 1 ml each.

SANDOSTATIN Vial 1 mg per 5 ml: Carton containing 1 multidose vial of 5 ml.

STORAGE INSTRUCTIONS

Keep container in the outer carton in order to protect from light.

For prolonged storage SANDOSTATIN ampoules and multidose vials should be kept at temperatures of 2 °C to 8 °C. Do not freeze.

For day-to-day use they may be stored at room temperature (not above 25 °C) for up to 2 weeks.

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

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

SANDOSTATIN Ampoule 0,05 mg per 1 ml: V/34/230

SANDOSTATIN Ampoule 0,1 mg per 1 ml: V/34/231

SANDOSTATIN Vial 1 mg per 5 ml: V/34/232

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View

Johannesburg

2090

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