Sandostatin®

Antigrowth hormone

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Solution for injection (s.c) or concentrate for solution for infusion (i.v.infusion).

The solution is clear and colourless.

Active substance(s)

The active substance is octreotide acetate.

1 mL ampoules containing 0.05, 0.1 or 0.5 mg octreotide (as free peptide).

5 mL multidose vials containing 1 mg octreotide (as free peptide).

Certain dosage strengths and dosage forms may not be available in all countries.

Excipients

Ampoules

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

Multidose vials

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

Pharmaceutical formulations may vary between countries.

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-entero-pancreatic (GEP) endocrine tumors:

- Carcinoid tumors with features of the carcinoid syndrome.
- VIPomas.
- Glucagonomas.
- Gastrinomas/Zollinger-Ellison syndrome, usually in conjunction with proton pump inhibitors, or H_2-antagonist therapy.
- Insulinomas, for pre-operative control of hypoglycemia and for maintenance therapy.
- GRFomas.

Sandostatin is not an anti-tumor therapy and is not curative in these patients.

Control of refractory diarrhea associated with AIDS.

Prevention of complications following pancreatic surgery.

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

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Acromegaly

Initially 0.05 to 0.1 mg by s.c. injection every 8 or 12 hours. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH < 2.5 ng/mL; IGF-1 within normal range) and clinical symptoms, and 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.

If no relevant reduction in IGF-1 and/or GH levels and no improvement in clinical symptoms have been achieved within 3 months of starting treatment with Sandostatin, therapy should be discontinued.

Gastro-entero-pancreatic endocrine tumors

Initially 0.05 mg once or twice daily by s.c. injection. Depending on clinical response, effect on levels of tumor-produced hormones (in cases of carcinoid tumors, on the urinary excretion of 5-hydroxyindole acetic acid), and on tolerability, dosage can be gradually increased to 0.1 to 0.2 mg 3 times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses have to be adjusted individually.

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

AIDS-related refractory diarrhea

The data suggest that 0.1 mg 3 times per day by s.c. injection is the optimal starting dose. If diarrhea is not controlled after 1 week of treatment, the dose should be titrated on an individual basis up to 0.25 mg 3 times per day. Dose adjustment should be based on assessment of stool output and on tolerability.

If within 1 week of treatment with Sandostatin at a dose of 0.25 mg 3 times per day no improvement is achieved, therapy should be discontinued.

Complications following pancreatic surgery

0.1 mg 3 times daily by s.c. injection for 7 consecutive days, starting on the day of operation at least 1 hour before laparotomy.

Bleeding gastro-esophageal varices

25 microgram/hour for 5 days by continuous i.v. infusion. Sandostatin can be used in dilution with physiological saline.

In cirrhotic patients with bleeding gastro-esophageal varices, Sandostatin has been well tolerated at continuous i.v. doses of up to 50 microgram/hour for 5 days (see section OVERDOSAGE).

Special populations

Hepatic impairment

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

Renal impairment

Impaired renal function did not affect the total exposure (AUC) to octreotide administered as s.c. injection, therefore no dose adjustment of Sandostatin is necessary.

Pediatric patients (below 18 years)

Experience with Sandostatin in children is limited.

Geriatric patients (65 years or above)

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients treated with Sandostatin.

CONTRAINDICATIONS

Known hypersensitivity to octreotide or to any of the excipients, (see section DESCRIPTION AND COMPOSITION).

WARNINGS AND PRECAUTIONS

General

As GH-secreting pituitary tumors may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients be carefully monitored. If evidence of tumor 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 octreotide (see section PREGNANCY, BREAST-FEEDING AND FERTILITY).

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

Cardiovascular related events

Cases of bradycardia have been reported (frequency: common). 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

Cholelithiasis is a very common event during Sandostatin treatment and may be associated with cholecystitis and biliary duct dilatation (see section ADVERSE DRUG REACTIONS). Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients taking Sandostatin in the post-marketing setting. Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during Sandostatin therapy is therefore recommended.

GEP endocrine tumors

During the treatment of GEP endocrine tumors, there may be rare instances of sudden escape from symptomatic control by Sandostatin, with rapid recurrence of severe symptoms.

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 hyperglycemia may be induced as a result of chronic administration. Hypoglycemia has also been reported.

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 during initiation of Sandostatin therapy and at each change of dosage. Marked fluctuations in blood glucose concentration may possibly be reduced by smaller, more frequently administered doses.

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, following bleeding episodes from esophageal varices, there is an increased risk 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.

Local site reactions

In a 52-week toxicity study in rats, predominantly in males, sarcomas were noted at the s.c. injection site only at the highest dose (about 40 times the maximum human dose). No hyperplastic or neoplastic lesions occurred at the s.c. injection site in a 52-week dog toxicity study. There have been no reports of tumor formation at the injection sites in patients treated

with Sandostatin for up to 15 years. All the information available at present indicates that the findings in rats are species specific and have no significance for the use of the drug in humans.

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin in patients who have a history of vitamin B_{12} deprivation.

ADVERSE DRUG REACTIONS

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 diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycemia 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 hypoglycemia.

Tabulated summary of adverse drug reactions from clinical trials

The following adverse drug reactions (ADRs), listed in Table 1, have been accumulated from clinical studies with octreotide:

Adverse drug reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with 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

Endocrine disorders	
Common:	Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased Total T4, and decreased Free T4).
Metabolism and nutrition disorders	
Very common:	Hyperglycaemia
Common:	Hypoglycaemia, glucose tolerance impaired, decreased appetite.
Uncommon:	Dehydration.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
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, faeces discolored.
Hepatobiliary disorders	
Very common:	Cholelithiasis.
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia,
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
General disorders and administration site conditions	
Very common:	Injection site reaction.
Common:	Asthenia
Investigations	
Common:	Transaminase increased.

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

The following adverse drug reactions have been derived from post-marketing experience with octreotide 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 from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders Thrombocytopenia
Immune system disorders Anaphylactic reaction, allergy/hypersensitivity reactions.
Cardiac disorders Arrhythmias.
Hepatobiliary disorders Pancreatitis acute, acute hepatitis without cholestasis**,** hepatitis cholestatic. Cholestasis, jaundice, jaundice cholestatic.
Skin and subcutaneous tissue disorders Urticaria.
Investigations Blood alkaline phosphatase increased, gamma glutamyl transferase increased.

Description of selected adverse drug reactions

Gastrointestinal disorders and nutrition

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

Although measured fecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide 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

Somatostatin 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 Sandostatin-treated patients is largely asymptomatic. Symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery. (See "Recommendation for the management of patients during Sandostatin treatment with respect to the development of gallstones" at the end of this document).

Injection site reactions

Pain or a sensation of stinging, tingling or burning at the site of s.c. injection can occur, 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 adverse reaction with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarization, 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 WARNINGS AND PRECAUTIONS).

Pancreatitis

Cholelithiasis-induced pancreatitis has been reported for patients on long-term Sandostatin s.c. treatment. 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.

Hypersensitivity and anaphylactic reactions

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

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.

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 section WARNINGS AND PRECAUTIONS).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin is administered concomitantly (see section WARNINGS AND PRECAUTIONS).

Sandostatin 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 analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g. quinidine, terfenadine).

PREGNANCY, BREAST-FEEDING AND FERTILITY

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 100-300 microgram/day of Sandostatin s.c. or 20-30 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.

Studies in laboratory animals have not shown reproductive toxicological effects. A transient growth retardation of offspring was observed in rats, possibly consequent upon the specific endocrine profile of the species tested (see section NON-CLINICAL SAFETY DATA)

Sandostatin should only be prescribed to pregnant woman under compelling circumstances (see section WARNINGS AND PRECAUTIONS).

Breast-feeding

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.

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 section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

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 microgram/day administered by continuous infusion (100-250 microgram/hour) or subcutaneously (1,500 microgram t.i.d.). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving higher doses of continuous infusion (100 microgram/hour) and/or bolus of Sandostatin intravenously (50 microgram bolus followed by 50 microgram/hour continuous infusion).

In children, the doses ranged from 50-3,000 microgram/day administered by continuous infusion (2.1-500 microgram/hour) or subcutaneously (50-100 microgram). The only adverse event reported was mild hyperglycemia.

No unexpected adverse events have been reported in cancer patients receiving Sandostatin at doses of 3,000-30,000 microgram/day in divided doses subcutaneously.

Treatment

The management of overdosage is symptomatic. Patients who received higher than recommended doses of intravenous octreotide are at increased risk of higher degree atrioventricular blocks and should be kept under appropriate cardiac monitoring.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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 Sandostatin has been shown to inhibit:

- release of GH stimulated by arginine, exercise- and insulin-induced hypoglycemia,
- postprandial 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 acromegalic patients Sandostatin lowers plasma levels of GH and IGF-1. A GH reduction by 50% or more occurs in up to 90% patients, and a reduction of serum GH to < 5 ng/mL can be achieved in about half of the cases. In most patients Sandostatin markedly reduces the clinical symptoms of the disease, such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paresthesia. In patients with a large pituitary adenoma, Sandostatin treatment may result in some shrinkage of the tumor mass.

In patients with functional tumors of the GEP endocrine system, Sandostatin, because of its diverse endocrine effects, modifies a number of clinical features. Clinical improvement and symptomatic benefit occur in patients who still have symptoms related to their tumors despite previous therapies, which may include surgery, hepatic artery embolization, and various chemotherapies, e.g. streptozotocin and 5-fluorouracil.

PHARMACODYNAMICS (PD)

Sandostatin's effects in the different tumor types are as follows

Carcinoid tumors

Administration of Sandostatin may result in improvement of symptoms, particularly of flush and diarrhea. 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 tumors is overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of Sandostatin results in alleviation of the severe secretory diarrhea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalemia, 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 tumor, or even tumor 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 Sandostatin results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of Sandostatin 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 hypoglycemic agents. Sandostatin produces improvement of diarrhea, and hence weight gain, in those patients affected. Although administration of Sandostatin 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

Although therapy with proton pump inhibitors or H_2-receptor blocking agents controls the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid, such control may be incomplete. Diarrhea may also be a prominent symptom not alleviated by this therapy. Sandostatin alone or in conjunction with proton pump inhibitors or H_2-receptor antagonists may reduce gastric acid hypersecretion and improve symptoms, including diarrhea. Other symptoms possibly due to peptide production by the tumor, e.g. flush, may also be relieved. Plasma gastrin levels fall in some patients.

Insulinomas

Administration of Sandostatin produces a fall in circulating immunoreactive insulin, which may, however, be of short duration (about 2 hours). In patients with operable tumors Sandostatin may help to restore and maintain normoglycaemia pre-operatively. In patients with inoperable benign or malignant tumors, glycemic control may be improved without concomitant sustained reduction in circulating insulin levels.

GRFomas

These rare tumors are characterized by production of GH releasing factor (GRF) alone or in conjunction with other active peptides. Sandostatin produces improvement in the features and symptoms of the resultant acromegaly. This is probably due to inhibition of GRF and GH secretion, and a reduction in pituitary enlargement may follow.

In patients with acquired immune deficiency syndrome (AIDS)-related refractory diarrhea, Sandostatin produces partial or complete control of stool output in about one-third of patients with diarrhea unresponsive to conventional anti-infective and/or antidiarrheal agents.

For patients undergoing pancreatic surgery, the peri- and post-operative administration of Sandostatin reduces the incidence of typical postoperative complications (e.g. pancreatic fistula, abscess and subsequent sepsis, postoperative acute pancreatitis).

In patients presenting with bleeding gastro-esophageal varices due to underlying cirrhosis, Sandostatin administration in combination with specific treatment (e.g. sclerotherapy) is associated with better control of bleeding and early re-bleeding, reduced transfusion requirements, and improved 5-day survival. While the precise mode of action of Sandostatin is not fully elucidated, it is postulated that Sandostatin reduces splanchnic blood flow through inhibition of vaso-active hormones (e.g. VIP, glucagon).

PHARMACOKINETICS (PK)

Absorption

After s.c. injection, Sandostatin is rapidly and completely absorbed. Peak plasma concentrations are reached within 30 minutes.

Distribution

The volume of distribution is 0.27 L/kg, and the total body clearance 160 mL/min. Plasma protein binding amounts to 65%. The amount of Sandostatin bound to blood cells is negligible.

Elimination

The elimination half-life after s.c. administration is 100 minutes. After i.v. injection, the elimination is biphasic, with half-lives of 10 and 90 minutes. Most of the peptide is eliminated via the feces, while approximately 32% is excreted unchanged into the urine.

Special patient population

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

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

CLINICAL STUDIES

Not applicable. Sandostatin is an established product.

NON-CLINICAL SAFETY DATA

Repeat-dose toxicity

An initial 26-week i.v. toxicity study in dogs carried out at dose levels of up to 0.5 mg/kg once daily revealed proliferative/degenerative changes in acidophil prolactin-containing cells in the pituitary. Further investigations showed this to be within the physiological range of the species used. Female Rhesus monkeys receiving 0.5 mg/kg twice daily (b.i.d) for 3 weeks failed to reveal pituitary changes, and there were no alterations of basal levels of plasma growth hormone, prolactin, or glucose.

Whereas the acidic vehicle produced inflammation and fibroplasia upon repeated s.c. injection in rats, there was no evidence that octreotide acetate causes delayed-type hypersensitivity reactions when injected intradermally in guinea pigs in 0.1% solution in 0.9% sterile saline.

Genotoxicity

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

Carcinogenicity/chronic toxicity

In rats receiving octreotide acetate at daily doses up to 1.25 mg/kg body weight, fibrosarcomas were observed, predominantly in a number of male animals, at the s.c. injection site after 52, 104 and 113/116 weeks. Local tumors occurred also in the control rats, however development of these tumors 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 octreotide at doses up to 2 mg/kg for up to 99 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. octreotide also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest s.c. dose level of 1.25 mg/kg per day. The finding was associated with an increased incidence of endometritis, a decreased number of ovarian corpora lutea, a reduction in mammary adenomas and the presence of uterine glandular and luminal dilation, suggesting a state of hormonal imbalance. The available information clearly indicates that the findings of endocrine-mediated tumors in rats are species-specific and are not relevant for the use of the drug in humans.

Reproduction

Reproduction studies have been performed in rats and rabbits at parenteral doses of up to 1 mg/kg body weight per day. Some retardation of 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. There was no evidence of teratogenic, embryo/fetal or other reproduction effects due to octreotide.

INCOMPATIBILITIES

Octreotide acetate is not stable in Total Parenteral Nutrition (TPN) solutions. It is generally not recommended to mix other medicinal products with octreotide in the same infusion bag or in the same cannula. Physical incompatibilities have been reported (e.g. with pantoprazole).

SPECIAL PRECAUTIONS FOR STORAGE

Ampoules

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

For prolonged storage, Sandostatin ampoules must be stored at 2 to 8°C.

Do not freeze.

For day-to-day use, they may be stored not above 30°C for up to 2 weeks.

Multidose vials

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

For prolonged storage, Sandostatin multidose vials must be stored at 2 to 8°C.

Do not freeze.

For day-to-day use, they may be stored not above 25°C for up to 2 weeks.

Sandostatin should not be used after the date marked “EXP” on the pack.

INSTRUCTIONS FOR USE AND HANDLING

Subcutaneous administration

Patients who are to self-administer the drug by s.c. injection must receive precise directions from the physician or the nurse.

To reduce local discomfort, it is recommended that the solution should be at 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 that the cap of multidose vials should be punctured not more than 10 times.

Intravenous infusion

Parenteral drug products should be inspected visually for discoloration and particulate matter prior to administration.

Sandostatin (octreotide acetate) is physically and chemically stable for 24 hours in sterile physiological saline 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 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 i.v. infusion, the contents of one 0.5 mg ampoule should normally be dissolved in 60 mL physiological saline, 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.

Special precautions for disposal

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

Note: Sandostatin should be kept out of the reach and sight of children.

Recommendation for the management of patients during Sandostatin treatment with respect to the development of gallstones.

1. Patients should undergo a baseline ultrasound examination of the gallbladder prior to commencing octreotide treatment.
2. Periodic repeat ultrasound examination of the gallbladder should be performed, preferably at about 6-month intervals, throughout Sandostatin treatment.
3. If stones are already present before the start of therapy, the potential benefit of Sandostatin should be assessed against the potential risks associated with the gallstones. There is no evidence at present that Sandostatin adversely affects the course or prognosis of pre-existing gallstones.
4. Management of patients who develop gallstones in association with Sandostatin:
    i. **Asymptomatic gallstones**

Sandostatin may be continued, depending on re-assessment of the benefit/risk ratio. Either way, no action is required except to continue monitoring, with increased frequency if this is considered necessary.

ii. **Symptomatic gallstones**

Sandostatin may be either stopped or continued, depending on re-assessment of the benefit/risk ratio. Either way, the gallstones should be treated like any other symptomatic gallstones. Medically, this may include combined bile acid therapy (e.g. chenodeoxycholic acid [CDCA] together with ursodeoxycholic acid [UDCA] or monotherapy with ursodeoxycholic acid (UDCA) associated with ultrasound monitoring until the stones have completely disappeared. For posology and treatment duration, please consult the locally approved prescribing information for CDCA and/or UDCA.

Manufacturer:

See folding box.

International Package Leaflet

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