AUSTRALIAN PRODUCT INFORMATION – SANDOSTATIN (OCTREOTIDE AS ACETATE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Octreotide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule contains 0.05 mg, 0.1 mg or 0.5 mg octreotide (present as acetate).

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection. The solution for injection is clear and colourless.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- For symptomatic control and reduction of growth hormone and IGF-1 plasma levels in patients with acromegaly, including those who are inadequately controlled by surgery, radiotherapy, or dopamine agonist treatment. Sandostatin treatment is also indicated in acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.
- For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system:
  - Carcinoid tumours with features of the carcinoid syndrome.
  - Vasoactive intestinal peptide secreting tumours (VIPomas).

Sandostatin is not curative in these patients.

- For reduction of the incidence of complications following pancreatic surgery.

4.2 DOSE AND METHOD OF ADMINISTRATION

Acromegaly

Initially 0.05-0.1 mg by subcutaneous 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 on clinical symptoms, and on tolerability. In most patients the optimal daily dose will be 0.2 to 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 biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with Sandostatin, therapy should be discontinued.

Gastro-entero-pancreatic endocrine tumours

Initially 0.05 mg once or twice daily by subcutaneous injection. Depending on clinical response, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 micrograms per day is limited.

Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

0.1 mg three times daily by subcutaneous injection for seven consecutive days, starting on the day of operation at least one hour before laparotomy.

Method of Administration

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

To reduce local discomfort, it is recommended that the solution reaches room temperature before injection. Multiple injections at short intervals at the same site should be avoided.

Single use. Contains no antimicrobial agent. Ampoules should be opened just prior to administration and any unused portion discarded.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Do not use if particulates and/or discolouration are observed.

Use in the elderly

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

Use in children

Experience with Sandostatin in children is very limited.

4.3 CONTRAINDICATIONS

Hypersensitivity to octreotide or to any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular related events

Cases of bradycardia have been reported (frequency: common). Medical review including dose adjustment of this agent and dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary.

Development of gallstones

Cholelithiasis is a very common event during Sandostatin treatment and may be associated with cholecystitis and biliary duct dilatation (see Section 4.8 Adverse Effects (Undesirable Effects)). 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 6 to 12 monthly intervals during Sandostatin therapy is therefore recommended.

GH secreting pituitary tumours

As GH secreting pituitary tumours may sometimes expand, thereby 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.

Gastro-entero-pancreatic 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.

Effects on glucose regulation

In patients with concomitant hypersecretion of insulin, Sandostatin, because of its greater relative potency in inhibiting secretion of growth hormone and glucagon than of insulin, and its shorter duration of action on inhibition of the latter, may increase the depth of, and prolong the duration of hypoglycaemia. Such patients should be closely observed on introduction of Sandostatin therapy and at each change of dosage. Marked fluctuations of blood glucose concentration may possibly be reduced by more frequent administration of Sandostatin.

Patients with type I diabetes mellitus requiring insulin therapy may have their insulin requirements reduced by administration of Sandostatin. In non-diabetic patients and patients with type II diabetes mellitus who have partially intact insulin reserves, Sandostatin administration can result in prandial increases in glycaemia (see Section 4.8 Adverse Effects (Undesirable Effects)). It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

Oesophageal varices

Sandostatin administration to patients who have concomitant bleeding gastro-oesophageal varices due to underlying hepatic cirrhosis increases the risk of development of insulin-dependent diabetes or of changes in insulin requirements in the presence of pre-existing diabetes. Therefore, appropriate monitoring of blood glucose levels is mandatory.

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.

Thyroid function

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

Use in hepatic impairment

In patients with liver cirrhosis, the half-life of the drug may be increased. If this occurs, adjustment of the maintenance dose may be considered.

Use in renal impairment

Impaired renal function did not affect the total exposure (AUC) to octreotide when administered subcutaneously. Therefore, no dose adjustment of Sandostatin is necessary.

Use in the elderly

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

Paediatric use

Experience with Sandostatin in children is very limited.

Effects on laboratory tests

See Section 4.4 subheading Nutrition earlier in this section.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Many patients with carcinoid syndrome or VIPomas being treated with Sandostatin have also been, or are being, treated with many other drugs to control the symptomatology or progression of the disease, including chemotherapeutic agents, H2 antagonists, antimotility agents, drugs affecting glycaemic states, solutions for electrolyte and fluid support or hyperalimentation, antihypertensive diuretics and anti-diarrhoeal agents.

Octreotide has been reported to produce a reduction in the intestinal absorption of cyclosporin, and a delay in 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 metabolised by cytochrome P450 enzymes, possibly due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs which are mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine) should be used with caution.

Since octreotide has also been associated with alterations in nutrient absorption, its effect on absorption of any orally administered drugs should be carefully considered.

Where symptoms are severe and Sandostatin therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta blockers, calcium channel blockers or agents for the control of fluid and electrolyte balance, patients must be monitored closely and adjustment made in the other therapies as the symptoms of the disease are controlled. Evidence currently available suggests these imbalances in fluid and electrolytes or glycaemic states are secondary to correction of pre existing abnormalities and not to a direct metabolic action of Sandostatin. Adjustment of the dosage of drugs, such as insulin, affecting glucose metabolism may be required during Sandostatin therapy (see Section 4.4 Special Warnings and Precautions for Use, subheading Effects on Glucose Regulation).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

It is not known whether octroetide has an effect on human fertility. Reproduction studies have been performed in rats and rabbits at doses up to 1 mg/kg octreotide and have revealed no evidence of any adverse effect of subcutaneous octreotide on fertility or morphogenesis (see Section 4.6 subheading Use in Pregnancy below).

Use in pregnancy – Pregnancy Category C

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.

Sandostatin should only be prescribed to pregnant women under compelling circumstances.

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

Reproduction studies have been performed in rats and rabbits at doses up to 1 mg/kg and have revealed no evidence of any adverse effect of Sandostatin on fertility or morphogenesis. Foetal and post-natal growth retardation was seen in rats, probably due to suppression of growth hormone.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety Profile

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

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

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (see Table 1 below) 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

Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence.
Common:	Dyspepsia, vomiting, abdominal distension, steatorrhoea, loose stools, faeces discoloured.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Endocrine disorders	
Common:	Hypothyroidism, thyroid disorder (e.g. decreased TSH, decreased Total T4, and decreased Free T4).
Hepatobiliary disorders	
Very common:	Cholelithiasis.
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia.
Metabolism and nutrition disorders*	
Very common:	Hyperglycaemia.
Common:	Hypoglycaemia, glucose tolerance impaired, anorexia.

Uncommon:	Dehydration.
General disorders and administration site conditions	
Very common:	Injection site reactions.
Common:	Asthenia
Investigations	
Common:	Transaminase increased.
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea.
Cardiac disorders	
Common:	Bradycardia.
Uncommon:	Tachycardia.

* 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. Hypoglycaemia has also been reported.

Flushing and oedema, events attributable to the underlying condition, have been observed.

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

The following adverse drug reactions (Table 2) 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 categorised 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 disorders	Anaphylactic reaction, allergy/hypersensitivity reactions.
Skin and subcutaneous tissue disorders	Urticaria.
Hepatobiliary disorders	Pancreatitis acute, acute hepatitis without cholestasis*, hepatitis cholestatic, cholestasis, jaundice, jaundice cholestatic.
Cardiac disorders	Arrhythmias.
Investigations	Blood alkaline phosphatase increased, gamma glutamyl transferase increased.

* Where there has been normalisation of transaminase values on withdrawal of subcutaneous octreotide.

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

Injection site reactions

Local reactions may occur and include pain, a sensation of stinging, tingling or burning at the site of injection, with redness, swelling, irritation and rash. They rarely last 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, arrhythmia and ECG changes such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes were observed. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see Section 4.4 Special Warnings and Precautions for Use, subheading Cardiovascular Related Events).

Pancreatitis

Acute pancreatitis has been reported in rare instances. Generally, the effect is seen within the first hours or days of Sandostatin treatment and resolves on withdrawal of the drug. In addition, pancreatitis may develop in patients on long-term Sandostatin treatment who develop gallstones.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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) over a period of 1 to 2 weeks or 3000 micrograms/day (1000 micrograms t.i.d. for 2 days) administered subcutaneously. Some of the adverse events reported included arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, 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, when Sandostatin was administered intravenously at a dose of 3000 micrograms/day (500 micrograms/hour) for 6 hours, mild hyperglycaemia was reported.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: anti-growth hormone

ATC code: H01CB02

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of 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 the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Sandostatin, like somatostatin, decreases splanchnic blood flow.

In animals, octreotide is a more potent inhibitor of growth hormone, 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 growth hormone (GH) stimulated by arginine, exercise and insulin-induced hypoglycaemia
- postprandial release of insulin, glucagon, gastrin, other peptides of the GEP system, and arginine stimulated release of insulin and glucagon
- thyrotropin releasing hormone (TRH) stimulated release of thyroid stimulating hormone (TSH).

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

In patients with acromegaly (including those who have failed to respond to surgery, radiation or dopamine agonist treatment), Sandostatin lowers plasma levels of GH and Insulin-like Growth Factor-1/Somatomedin C (IGF-1). A reduction in plasma GH (by 50% or more) occurs in almost all patients, and a plasma GH < 5 ng/mL can be achieved in about half of the cases. Most patients with symptoms such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paraesthesia report a reduction in these symptoms. In patients with a large pituitary adenoma, Sandostatin treatment may result in some shrinkage of the tumour mass.

In patients with functional tumours of the gastro-entero-pancreatic endocrine system, Sandostatin, because of its diverse endocrine effects, modifies different clinical features. Clinical improvement and symptomatic benefit occur in patients who have severe symptoms related to their tumours despite

previous therapies which include surgery, hepatic artery embolisation and various chemotherapies, e.g. streptozotocin and 5-fluorouracil.

Sandostatin's effects in the different tumour types are as follows:

- Carcinoid tumours:

  Administration of Sandostatin may result in improvement of symptoms, particularly of flush episodes and severe diarrhoea. In some cases this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5 hydroxyindole acetic acid. In the event of no beneficial response to Sandostatin treatment, continuation of therapy beyond one week at the maximum tolerated dose is not recommended, although in non responders no serious sustained adverse drug effects have been reported.

- Vasoactive intestinal peptide secreting tumours (VIPomas):

  The biochemical characteristic of these tumours is overproduction of vaso-active intestinal peptide (VIP). In most cases, administration of Sandostatin 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.

In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin LAR on tumour size, rate of growth and development of metastases, has not been determined.

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

A large multi centre study in patients with acute bleeding due to gastric or duodenal ulcer showed no benefit of Sandostatin over placebo in the control of haemorrhage.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 microgram dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after s.c. administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80- 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations

and area under the curve values were dose proportional both after s.c. or i.v. single doses up to 400 micrograms and with multiple doses of 200 micrograms t.i.d. (600 micrograms/day). Clearance was reduced by about 66% suggesting non linear kinetics of the drug at daily doses of 600 micrograms/day as compared to 150 micrograms/day. The relative decrease in clearance with doses above 600 micrograms/day is not defined.

Distribution

The distribution of octreotide from plasma was rapid (t½α = 0.2 h) and the volume of distribution after i.v. dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

Excretion

The elimination of octreotide from plasma had an apparent half-life of 1.5 hours compared with 1 to 3 minutes with the natural hormone. The duration of action of Sandostatin is variable but extends up to 12 hours depending upon the type of tumour. About 32% of the dose is excreted unchanged into the urine.

Effect of renal and hepatic dysfunction on pharmacokinetics:

Impaired renal function did not affect the total exposure (AUC) to octreotide administered as a subcutaneous injection. Therefore, no dose adjustment is necessary. In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in normal subjects (from approximately 10 L/h to 4.5 L/h).

The elimination capacity may be reduced in patients with liver cirrhosis (see Section 4.4 Special Warnings and Precautions for Use, subheading Use in hepatic Impairment) but not in patients with fatty liver disease.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 (see Section 4.6 Fertility, Pregnancy and Lactation, subheading Use in Pregnancy). 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.

Carcinogenicity

In repeat dose toxicity studies in rats of 52 weeks duration and longer, predominantly in males, sarcomas were noted at the subcutaneous injection site of octreotide in an acidic vehicle and at a lower incidence with the acidic vehicle alone. These did not occur in a mouse carcinogenicity study, nor did hyperplastic or neoplastic lesions occur at the subcutaneous injection site in a 52-week dog toxicity study. There have been no reports of tumour formation at the injection sites in patients treated for up to 15 years with Sandostatin. All information available at present indicates that the finding of injection site sarcomas in rats is species-specific and has no significance for the use of the drug in humans. The 116-week rat carcinogenicity study also revealed uterine endometrial adenocarcinomas, their incidence reaching

statistical significance at the highest dose of 1.25 mg/kg per day. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumours were associated with oestrogen dominance in the aged female rats which does not occur in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: lactic acid, mannitol, sodium bicarbonate, water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2 - 8°C (Refrigerate. Do not freeze). Protect from light. For day-to-day use Sandostatin may be stored at room temperature (below 30°C) for up to 2 weeks. Any ampoules unused after this period out of the refrigerator should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

Sandostatin solution for injection is packed in a 1 mL colourless glass ampoule with two colour code rings and a one-point cut.

0.05 mg octreotide in 1 mL comes in a box of 5 ampoules.

0.1 mg octreotide in 1 mL comes in a box of 5 ampoules.

0.5 mg octroetide in 1 mL comes in a box of 5 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

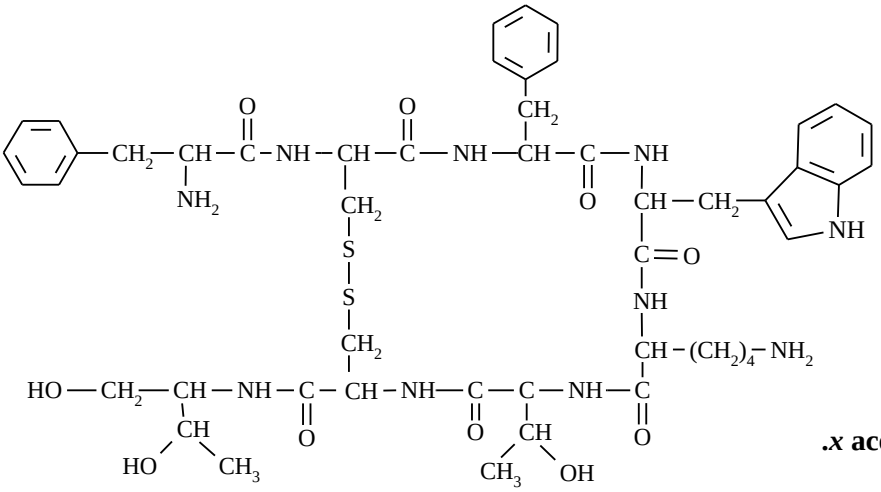
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2 → 7) – disulfide.

MW: 1019.3 (free peptide).

Chemical structure



***.x* acetate**

where x = 1.4 to 2.5

CAS number

79517-01-4. (octreotide acetate).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

05 January 1993

10 DATE OF REVISION

24 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial corrections (localised spelling, correction of typos, addition of cross-references).
5	Addition of ATC code and Pharmacotherapeutic group.