AUSTRALIAN PRODUCT INFORMATION – OCTREOTIDE DEPOT (OCTREOTIDE) MODIFIED RELEASE INJECTION

1 NAME OF THE MEDICINE

Octreotide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OCTREOTIDE DEPOT octreotide (as acetate) 10 mg modified release injection plus diluent

OCTREOTIDE DEPOT octreotide (as acetate) 20 mg modified release injection plus diluent

OCTREOTIDE DEPOT octreotide (as acetate) 30 mg modified release injection plus diluent

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

3 PHARMACEUTICAL FORM

Modified release, injection

Octreotide Depot is a modified release injection of octreotide. The octreotide is distributed within polymer microspheres. The powder is a white to white with yellowish tint.

Diluent

The vehicle is a clear, colourless to slightly yellow or brown solution. The pH of the reconstituted suspension is 5-8.

Single glass vials of 10, 20 or 30 mg octreotide modified release injection to be suspended in 2 mL diluent prior to injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Acromegaly

For the 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 but who are adequately controlled on s.c. treatment with octreotide. Octreotide Depot is also indicated in acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.

Gastro-entero-pancreatic tumours

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) in patients who are adequately controlled on subcutaneous treatment with octreotide

Octreotide Depot is not curative in these patients.

Advanced Neuroendocrine Tumours of the Midgut

Treatment of patients with progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Octreotide Depot may only be administered by deep intragluteal injection. Each injection is for single use only. The site of repeat intragluteal injections should be alternated between the left and right gluteal muscle. Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.

Acromegaly

Patients controlled with subcutaneous octreotide

In patients who are adequately controlled with the usual therapeutic range of subcutaneous octreotide, it is recommended to start treatment with the administration of 20 mg Octreotide Depot at 4-week intervals for 3 months. Treatment with Octreotide Depot can be started the day after the last dose of s.c. octreotide. Subsequent dosage adjustment should be based on serum GH and IGF- 1 concentrations and clinical symptoms.

In patients in whom clinical symptoms and biochemical parameters (GH; IGF-1) are not fully controlled (GH concentrations still above 2.5 µg/L) within this 3-month period, the dose may be increased to 30 mg every 4 weeks.

The monitoring of GH concentrations is recommended for another 3 months. If, after 6 months of treatment, the response is judged to be inadequate from clinical and biological points of view, Octreotide Depot should be discontinued.

For patients whose GH concentrations are consistently below 1 µg/L, whose IGF-1 serum concentrations are normalised, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg of Octreotide Depot 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, as well as clinical signs/symptoms at this low dose of Octreotide Depot.

For patients on a stable dose of Octreotide Depot, assessment of biochemical markers should be made periodically.

Patients not previously treated with octreotide

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 treatment period of subcutaneous octreotide is recommended to assess the response and systemic tolerability of octreotide prior to initiating treatment with Octreotide Depot as described above.

Gastro-entero-pancreatic endocrine tumours

Patients controlled with subcutaneous octreotide

For patients whose symptoms are adequately controlled with s.c. octreotide, it is recommended to start treatment with the administration of 20 mg Octreotide Depot at 4-week intervals. The treatment with s.c. octreotide should be continued at the previously effective dosage for 2 weeks after the first injection of Octreotide Depot.

For patients in whom symptoms and biological markers are well controlled after 3 months of treatment, the dose may be reduced to 10 mg Octreotide Depot every 4 weeks. For patients whose symptoms are only partially controlled after 3 months of treatment, the dose may be increased to 30 mg Octreotide Depot every 4 weeks.

For days when symptoms associated with gastro-entero-pancreatic tumours may increase during treatment with Octreotide Depot, additional administration of s.c. octreotide is recommended at the dose used prior to the Octreotide Depot treatment. This may occur mainly in the first 2 months of treatment until therapeutic concentrations of octreotide are reached.

Patients not previously treated with octreotide

For patients who were not previously treated with s.c. octreotide, it is recommended to start with the administration of s.c. octreotide at a dosage of 0.1 mg (100 micrograms) three times daily for a short period (approximately 2 weeks) to assess the response and systemic tolerability of octreotide before initiating the treatment with Octreotide Depot as described above.

Advanced neuroendocrine tumours of the midgut or suspected midgut origin

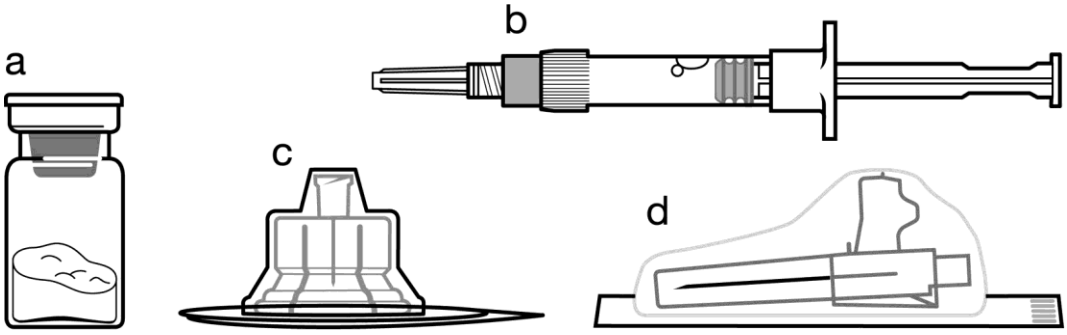
The recommended dose of Octreotide Depot is 30 mg administered every 4 weeks. Treatment with Octreotide Depot for tumour control should be continued in the absence of tumour progression.

Instructions for preparation and intramuscular injection for Octreotide Depot

Procedure Kit with vial adapter and safety needle

FOR DEEP INTRAGLUTEAL INJECTION ONLY
The reconstituted suspension contains no preservative. This medicine is for single use in one patient only. Discard any residue.

Content:



a. One vial containing Octreotide Depot powder,
b. One prefilled syringe containing the vehicle solution for reconstitution,
c. One vial adapter for drug product reconstitution,
d. One safety injection needle.

Follow the instructions below carefully to ensure proper reconstitution of Octreotide Depot before deep intragluteal injection.

There are 3 critical actions in the reconstitution of Octreotide Depot. **Not following them could result in failure to deliver the drug appropriately.**

- **The injection kit must reach room temperature**. Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the diluent solution, **ensure that the powder is fully saturated** by letting the vial stand for 5 minutes.
- After saturation, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until a uniform suspension is formed.** The Octreotide Depot suspension must only be prepared **immediately** before administration.

Octreotide Depot should only be administered by a trained health professional.

Step 1

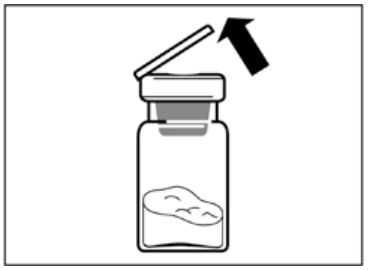
- Remove the Octreotide Depot injection kit from refrigerated storage.

ATTENTION: It is essential to start the reconstitution process only after the injection kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.

Note: The injection kit can be re-refrigerated if needed.

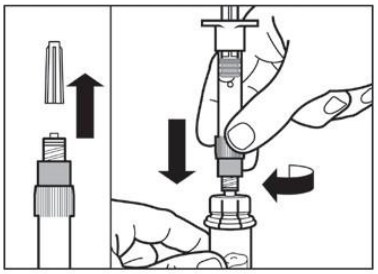
Step 2

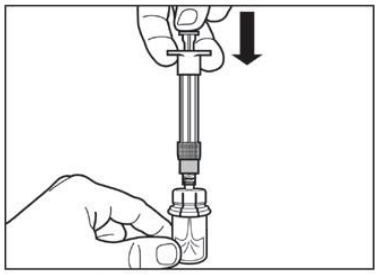
- Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.
- Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.
- Holding the vial adapter packaging, position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible “click.”
- Lift the packaging off the vial adapter with a vertical movement.



Step 3

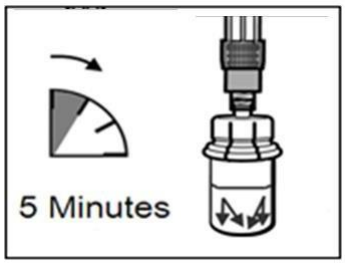
- Remove the cap from the syringe prefilled with diluent solution and screw the syringe onto the vial adapter.
- Slowly push the plunger all the way down to transfer all the diluent solution in the vial.





Step 4

ATTENTION: It is essential to let the vial stand for 5 minutes to ensure that the diluent has fully saturated the powder.

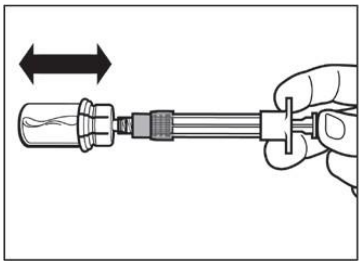


Note: It is normal if the plunger rod moves up as there might be a slight overpressure in the vial.

- At this stage prepare the patient for injection.

Step 5

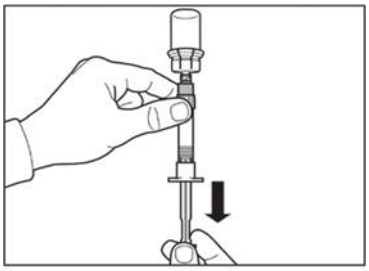
- After the saturation period, make sure that the plunger is pushed all the way down in the syringe.

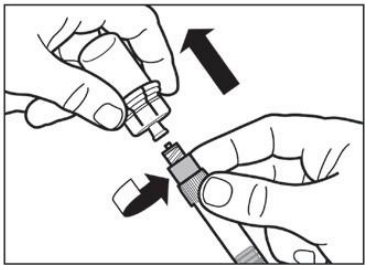


ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction for a **minimum of 30 seconds** so that the powder is completely suspended (milky uniform suspension). **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**

Step 6

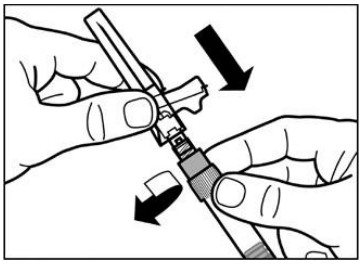
- Prepare injection site with an alcohol wipe.
- Turn syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe.
- Unscrew the syringe from the vial adapter.





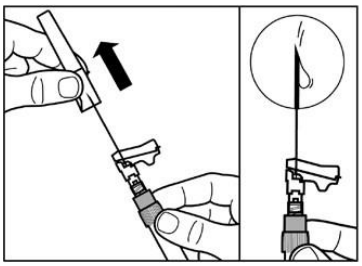
Step 7

- Screw the safety injection needle onto the syringe.
- Gently re-shake the syringe to ensure a milky uniform suspension.
- Pull the protective cover straight off the needle.
- Gently tap the syringe to remove any visible bubbles and expel them from the syringe. Verify that injection site has not been



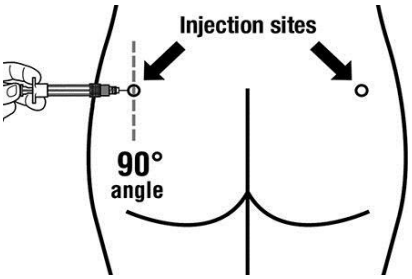
contaminated.

- Proceed **immediately** to Step 8 for administration to the patient. Any delay may result in sedimentation



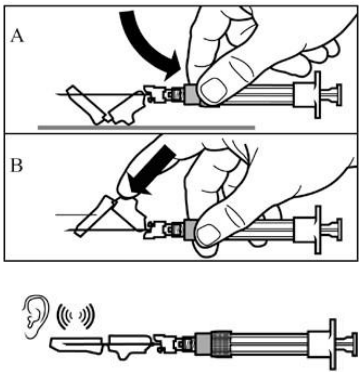
Step 8

- Octreotide Depot must be given only by deep intragluteal injection, **NEVER** intravenously.
- Insert the needle fully into the left or right gluteus at a 90º angle to the skin.
- Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).
- Depress the plunger with steady pressure until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in **Step 9**).



Step 9

- Activate the safety guard over the needle in one of the 2 methods shown:
  - either press the hinged section of the safety guard down onto a hard surface (figure A)
  - or push the hinge forward with your finger (figure B).
- An audible “click” confirms the proper activation.
- Dispose of syringe immediately (in a sharps container).



4.3 CONTRAINDICATIONS

Hypersensitivity to octreotide or any components 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.

Gallbladder and related events

Cholelithiasis is a very common event during octreotide 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 octreotide modified release injection in the post-marketing setting. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during Octreotide Depot therapy is recommended.

GH secreting pituitary tumours

As GH-secreting pituitary tumours may sometimes expand, causing serious complication (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 tumours

In the treatment of gastro-entero-pancreatic endocrine tumours with subcutaneous octreotide , sudden escape from symptomatic control may occur infrequently, with rapid recurrence of severe symptoms. To date, in patients with gastro-entero-pancreatic endocrine tumours treated with Octreotide Depot, there is no evidence of a sudden escape from symptomatic control with abrupt recurrence of severe symptoms.

Effects on glucose regulation

In patients with concomitant Type I diabetes mellitus, Octreotide Depot is likely to affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and type II diabetics with partially intact insulin reserves, octreotide 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 concomitant hypersecretion of insulin, 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 Octreotide Depot in patients who have a history of vitamin B12 deprivation.

Thyroid function

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

Use in hepatic impairment

In a study with octreotide administered subcutaneously and intravenously it was shown that the elimination capacity was 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 Octreotide Depot is necessary in patients with liver cirrhosis.

Use in renal impairment

Impaired renal function did not affect the total exposure (AUC) to octreotide when administered

subcutaneously. Therefore, no dose adjustment of Octreotide Depot is necessary.

Use in the elderly

In a study with octreotide administered subcutaneously no dose adjustment was necessary in patients 65 years of age or older. Therefore, no dose adjustment is necessary in this group of patients with Octreotide Depot.

Paediatric use

There is very limited experience with the use of Octreotide Depot in children.

Effects on laboratory tests

See Section 4.4 Special warnings and precautions for use, Nutrition.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Octreotide Depot is administered concomitantly (see Section 4.4 Special warnings and precautions for use).

Octreotide has been found to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine. Since octreotide has also been associated with alterations in nutrient absorption, its effect on absorption of any orally administered drugs should be carefully considered.

Adjustment of the dosage of drugs affecting glucose metabolism, such as insulin and oral hypoglycaemic agents, may be required during Octreotide Depot therapy.

Concomitant administration of octreotide and bromocriptine increased 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) should therefore be used with caution.

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, Fertility, Pregnancy and Lactation, Use in Pregnancy).

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 octreotide s.c. or 20 to 30 mg/month of Octreotide Depot. 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.

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

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.

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. 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 excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during octreotide 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) from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

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, Octreotide Depot may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with s.c. octreotide, in some instances, a state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

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. Adverse drug reactions 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 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

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

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. In clinical trials (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received octreotide for 12 months or longer was 52%. Less than 2% of patients treated with octreotide for 1 month or less developed gallstones.

The prevalence in the general population (aged 40 to 60 years) is estimated from reviews to be about 5-20%. Long-term exposure of patients with acromegaly or gastro-entero-pancreatic tumours to octreotide modified release injection suggests that treatment with Octreotide Depot does not increase the incidence of gallstone formation as compared to subcutaneous treatment. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Pancreatitis

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

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 however not established because many of these patients have underlying cardiac diseases (see Section 4.4 Special warnings and precautions for use).

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.

Injection site reactions

Local injection site reactions to Octreotide Depot may occur, and are usually mild and of short duration. They include local pain and, occasionally, swelling, irritation and rash.

Thrombocytopenia

Thrombocytopenia has been reported during post-marketing experience, particularly during treatment with octreotide (i.v.) in patients with cirrhosis of the liver, and during treatment with Octreotide Depot. 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

Symptoms

A limited number of accidental overdoses of octreotide 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 t.i.d.). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, heptomegaly and lactic acidosis.

A limited number of accidental overdoses of octreotide modified release injection have been reported. The doses ranged from 100 mg to 163 mg/month of octreotide modified release injection. The only adverse event reported was hot flushes.

Cancer patients receiving doses of octreotide modified release injection 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.

Treatment

The management of overdosage is symptomatic.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

- release of 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 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, Octreotide Depot, an injectable 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 Insulin-like Growth Factor-1/Somatomedin-C (IGF-1) serum concentrations in the majority of patients. In most patients, Octreotide Depot markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paraesthesia, fatigue, osteoarthralgia and carpal tunnel syndrome.

For patients with functional tumours of the gastro-entero-pancreatic endocrine system, treatment with Octreotide Depot 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.

Vasoactive intestinal peptide secreting tumours (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.

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 (GEP) peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

Clinical trials

Acromegaly

Octreotide modified release injection was evaluated in three clinical trials in acromegalic patients. In these studies, greater than 50% of patients achieved satisfactory serum concentrations of GH (< 2.5 ng/mL) and IGF-1 (< 500 ng/mL). In two of the clinical trials and their open-label extensions, a total of 101 patients were entered who had, in most cases, achieved a GH level < 5 ng/mL on subcutaneous octreotide given in doses of 100 micrograms or 200 micrograms three times a day. Most patients were switched to 20 mg or 30 mg doses of octreotide modified release injection given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well-controlled with

octreotide modified release injection as they had been on subcutaneous octreotide and this level of control remained for the entire duration of the trials.

A third trial was a 12 month open-label study that enrolled 151 patients who had GH level < 10 ng/mL after treatment with subcutaneous octreotide (most had levels < 5 ng/mL). The starting dose of octreotide modified release injection was 20 mg every 4 weeks for three doses. Thereafter, patients received 10, 20 or 30 mg every 4 weeks depending on the degree of GH suppression. Growth hormone and IGF-1 were at least as well controlled on octreotide modified release injection as they had been on subcutaneous octreotide. For the 122 patients who received all 12 injections in this trial, a mean GH level of 2.5 ng/mL was observed in 66% receiving octreotide modified release injection. Over the course of the trial, 57% of patients maintained mean growth hormone levels of < 2.5 ng/mL and mean normal IGF-1 levels.

Antibodies to octreotide have been noted in some patients (up to 25%) after treatment with octreotide. Such antibody positive patients were also observed in two clinical studies with octreotide modified release injection. The results for these patients suggest that there are no significant differences in efficacy and local or systemic tolerability between antibody positive and antibody negative subjects.

Two exploratory open label phase IV studies investigated a 24- and 48- week treatment with octreotide modified release injection in previously untreated acromegalic patients. The median reduction in tumour volume was 20.6% in study B2402 at 24 weeks (n=46) and 29.9% at 48 weeks (n=29) and 24.5% in study B2401 at 24 weeks (n=91) and 36.2% at 48 weeks (n=84). The percentage change in tumour volume during the course of the investigation was assessed by MRI for the intent-to-treat population.

Carcinoid syndrome

A six-month parallel group clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to subcutaneous octreotide. Sixty-seven patients were randomised at baseline to receive, double-blind doses of 10 mg, 20 mg or 30 mg octreotide modified release injection every 28 days and 26 patients continued, unblinded, on their previous subcutaneous octreotide regimen (100 to 300 micrograms three times a day). Octreotide modified release injection was as efficacious as subcutaneous octreotide in the control of the symptoms of carcinoid syndrome (diarrhoea, flushing). In patients treated with octreotide modified release injection , the need for supplementary doses of subcutaneous octreotide was comparable to that seen in the patients that continued on subcutaneous octreotide , but was somewhat higher in the 10 mg per 28 day group for the first few months.

In patients with carcinoid syndrome and VIPomas, the effect of octreotide modified release injection on tumour size, rate of growth and development of metastases, has not been determined.

Advanced neuroendocrine tumours of the midgut or unknown primary tumour location

An interim analysis of Phase III, randomised, double blind, placebo-controlled study (PROMID) demonstrated that octreotide modified release injection prolongs TTP in patients with advanced, well-differentiated Neuroendocrine Tumours of the midgut as compared to placebo, across all 3 efficacy analysed populations.

No conclusions could be drawn from the PROMID study regarding an important secondary endpoint;

overall survival.

85 patients were randomised to receive octreotide modified release injection 30 mg every 4 weeks (n = 42) or placebo (n = 43) for 18 months, or until tumour progression or death.

Main inclusion criteria were: treatment naïve; histologically confirmed; locally inoperable or metastatic well-differentiated; functionally active or inactive neuroendocrine tumors/carcinomas; with primary tumour located in the midgut or unknown origin believed to be of midgut origin if a primary within the pancreas, chest, or elsewhere was excluded.

The primary endpoint was time to tumor progression or tumor-related death (TTP). The TTP results by analysis populations is presented in Table 3 and described below.

In the intent-to-treat analysis population (ITT) (all randomised patients), 26 and 41 progressions or tumour-related deaths were seen in the octreotide modified release injection and placebo groups, respectively (HR = 0.32; 95% CI, 0.19 to 0.55; p-value =0.000015).

In the conservative ITT (cITT) analysis population in which 3 patients were censored at randomisation, 26 and 40 progressions or tumour-related deaths were observed in the octreotide modified release injection and placebo groups, respectively (HR=0.34; 95% CI, 0.20 to 0.59; p-value =0.000072; Fig 1).

Median time to tumour progression was 14.3 months (95% CI, 11.0 to 28.8 months) in the octreotide modified release injection group and 6.0 months (95% CI, 3.7 to 9.4 months) in the placebo group.

In the Per-protocol analysis population (PP) in which additional patients were censored at end study therapy, tumour progression or tumour-related death was observed in 19 and 38 octreotide modified release injection and placebo recipients, respectively (HR = 0.24; 95% CI, 0.13 to 0.45; p-value =0.0000036).

Table 3 TTP results by analysis populations

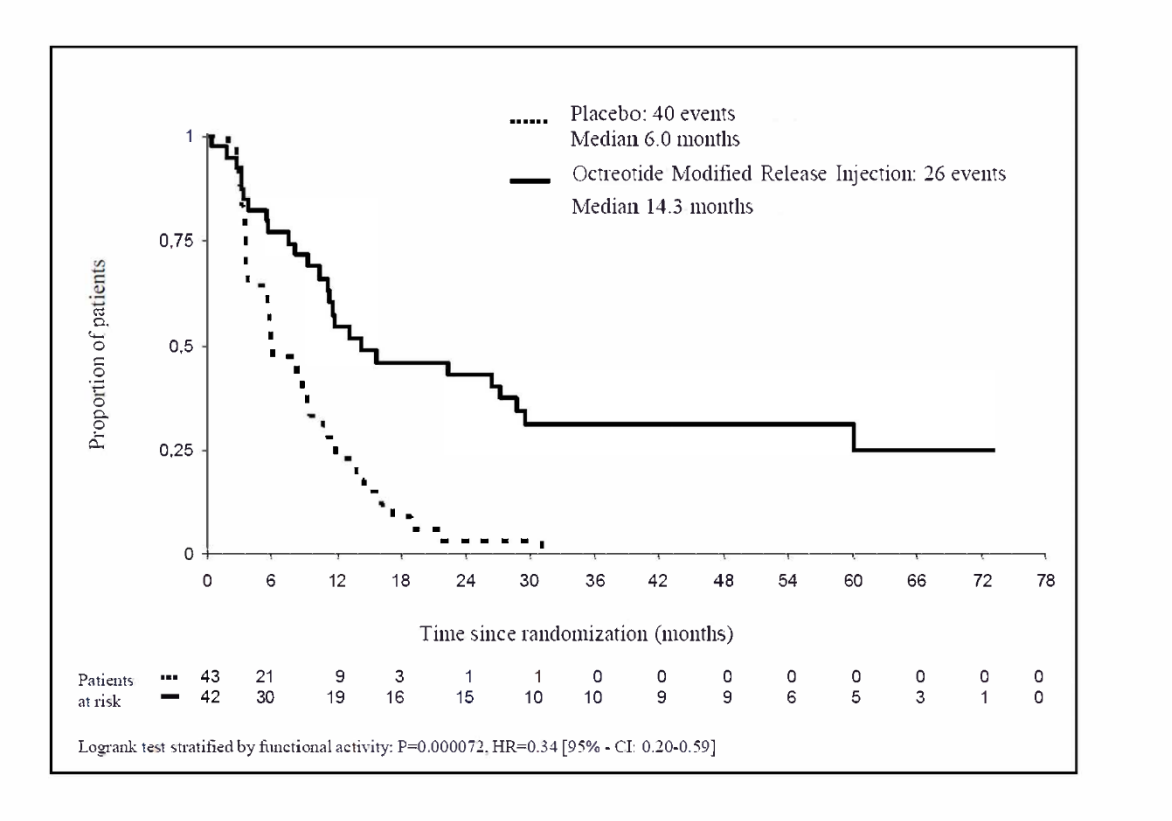
	TTP Events		**Median TTP months [95% C.I.]**		**HR [95% C.I.]** **p-value ***
	Octreotide modified release injection	**Placebo**	**Octreotide modified release injection**	**Placebo**	
ITT	26	41	NR	NR	0.32 [95% CI, 0.19 to 0.55] P=0.000015
cITT	26	40	14.3 [95% CI, 11.0 to 28.8]	6.0 [95% CI, 3.7 to 9.4]	0.34 [95% CI, 0.20 to 0.59] P=0.000072
PP	19	38	NR	NR	0.24

					[95% CI, 0.13 to 0.45] P =0.0000036

NR=not reported; HR=hazard ratio; TTP=time to tumour progression; ITT=intention to treat; cITT=conservative ITT; PP=per protocol

*Logrank test stratified by functional activity

Figure 1 Kaplan-Meier estimates of TTP comparing Octreotide modified release injection with placebo (conservative ITT population)



Subgroup analyses on the per-protocol analysis population demonstrated that treatment effect was similar in patients with functionality active (HR=0.23; 95% CI, 0.09 to 0.57), or inactive tumours (HR=0.25; 95% CI, 0.10 to 0.59).

After 6 months of treatment, stable disease was observed in 66 % of patients in the octreotide modified release injection group and 37 % of patients in the placebo group.

Both treatment groups had comparable levels of global QoL at random assignment and after 6 months of follow up.

Based on the significant benefit of octreotide modified release injection observed in this pre-planned interim analysis the recruitment was stopped, after over half (52%) of its intended participants were enrolled (85/162).

In this study, there were limitations in the estimation of the true magnitude of time to tumor progression and disease stabilisation with octreotide modified release injection . Documented progressive disease was not a requirement for study entry and there was a significant imbalance between the groups in time since diagnosis which was a median 7.5 months in the octreotide

modified release injection group and 3.3 months in the placebo group (p=0.01). As the treatment effect was relatively large after analysis of tumour progression or tumour related death in the analysed populations, these factors are not likely to affect the significance of the result.

The safety of octreotide modified release injection in this trial was consistent with its established safety profile.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After a single i.m. injection of octreotide modified release injection, the octreotide serum concentration reaches a peak within 1 hour after administration, the area under the peak not being larger than 0.5% of the total AUC, followed by a progressive decrease to low octreotide levels within 24 hours. After this initial peak, the octreotide concentration remains at sub-therapeutic levels for the majority of the patients for the following 7 days after the injection of octreotide modified release injection. This initial peak is lower than that observed when administering octreotide subcutaneously. Octreotide levels necessary for relevant and significant suppression of hormone secretion build up subsequently and remain quite stable from days 14 to 42. After day 42, the octreotide concentration decreases slowly.

In patients with acromegaly, mean plateau octreotide concentrations are about 358 ng/L, 926 ng/L and 1710 ng/L for single 10 mg, 20 mg and 30 mg dose respectively. Steady-state octreotide serum concentrations, reached after 3 injections at 4-week intervals, are higher by a factor of 1.6 to 1.8 (when determined on day 28 after the third injection) as compared to the plateau octreotide levels noted after the first injection (at day 28). During the plateau phase, the peak-trough fluctuation is much lower than that observed for subcutaneously administered octreotide. Octreotide did not accumulate in the body, as monitored over a duration of up to 28 monthly injections of octreotide modified release injection.

In patients with carcinoid tumours, the mean (and median) steady-state serum concentrations of octreotide after multiple injections of 10 mg, 20 mg and 30 mg of octreotide modified release injection 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.

Following doses of 20 and 30 mg octreotide modified release injection, the bioavailability of octreotide in cholecystectomized volunteers (measured over 107 days) relative to that seen after the same total doses of subcutaneously administered octreotide was shown to be 60% and 63%, respectively.

Distribution

According to data obtained with intravenously administered octreotide, the volume of distribution of octreotide is 0.27 L/kg. 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

According to data obtained with intravenously and subcutaneously administered octreotide, the total body clearance is 160 mL/min.

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, 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 3 years with subcutaneous octreotide. 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

Modified release injection
Polyglactin
Mannitol

Diluent

Carmellose sodium
Poloxamer
Mannitol
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

Storage Conditions: Store at 2 to 8°C. Do not freeze. Protect from light. Octreotide Depot can remain

below 25°C on the day of injection. **However, the suspension must only be prepared immediately prior to injection**.

6.5 NATURE AND CONTENTS OF CONTAINER

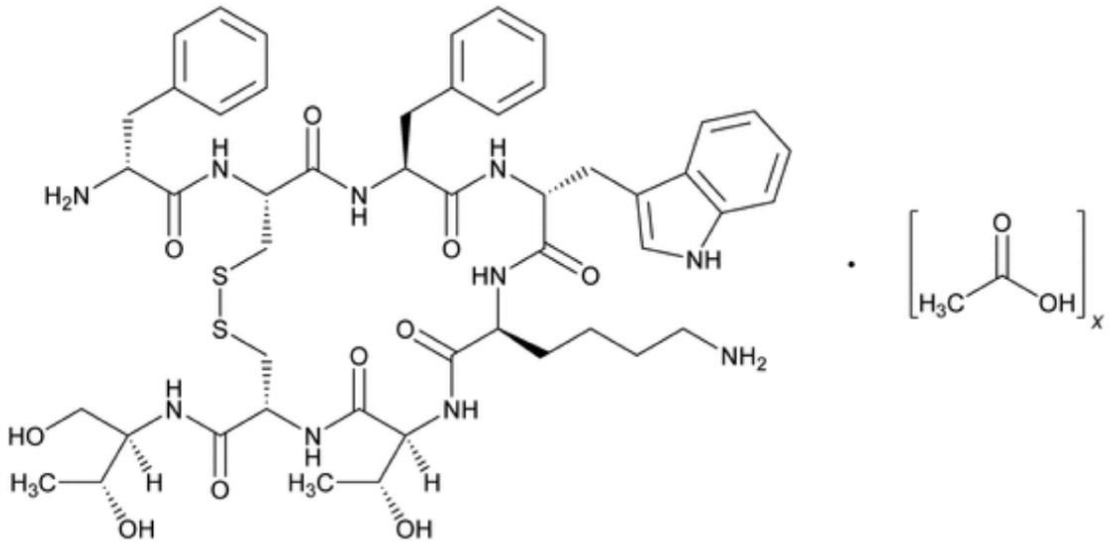
Each composite pack contains one 8 mL glass vial of powder, one 3 mL prefilled glass syringe containing 2 mL diluent, one vial adaptor and one safety injection needle. Vial contents to be suspended in diluent prior to injection.

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 structure



where *x* = 1.4 to 2.5

Molecular Weight: 1019.3 (free peptide)
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) – disulphide

CAS number

79517-01-4 (as acetate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Teva Pharma Australia Pty Ltd

Level 1, 37 Epping Road

Macquarie Park NSW 2113

AUSTRALIA

9 DATE OF FIRST APPROVAL

25th November 2020

10 DATE OF REVISION

25 May 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Vial size corrected to 8 mL