NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Octreotide Depot, 10 mg, Powder for Suspension for Injection (Teva)
Octreotide Depot, 20 mg, Powder for Suspension for Injection (Teva)
Octreotide Depot, 30 mg, Powder for Suspension for Injection (Teva)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg, 20 mg or 30 mg octreotide (as octreotide acetate).

Upon reconstitution of the vial with the 2 mL diluent, prefilled syringe results in the suspension for injection corresponding to the following concentrations:

- Octreotide Depot, 10 mg: Each vial contains 10 mg octreotide corresponding to 5 mg octreotide per mL.
- Octreotide Depot, 20 mg: Each vial contains 20 mg octreotide corresponding to 10 mg octreotide per mL.
- Octreotide Depot, 30 mg: Each vial contains 30 mg octreotide corresponding to 15 mg octreotide per mL.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder for Suspension for Injection and diluent.

- Powder: White to off-white powder for suspension for injection.
- Diluent: Clear colourless solution.

Octreotide Depot is a long-acting depot injection form of octreotide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- Treatment of patients with acromegaly:
    - in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective.

- Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumours:
    - Carcinoid tumours with features of the carcinoid syndrome.
    - VIPomas.
    - Glucagonomas.
    - Gastrinomas/Zollinger-Ellison syndrome.
    - Insulinomas, for pre-operative control of hypoglycaemia and for maintenance therapy.
    - GRFomas.

- 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

Dose

Acromegaly
It is recommended to start treatment with the administration of 20 mg Octreotide Depot at 4-week intervals for 3 months. Patients on treatment with subcutaneous octreotide can start treatment with Octreotide Depot the day after the last dose of subcutaneous octreotide. Subsequent dosage adjustment should be based on serum growth hormone (GH) and insulin-like growth factor 1/somatomedin C (IGF-1) concentrations and clinical symptoms.

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

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

For patients on a stable dose of Octreotide Depot, assessment of GH and IGF-1 should be made every 6 months.

Gastro-entero-pancreatic endocrine tumours
Treatment of patients with symptoms associated with functional gastro-entero-pancreatic neuroendocrine tumours

It is recommended to start treatment with the administration of 20 mg Octreotide Depot at 4-week intervals. Patients on treatment with subcutaneous octreotide should continue 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 in whom 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 subcutaneously 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.

Treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded

The recommended dose of Octreotide Depot is 30 mg administered every 4 weeks (see Section 5.1). Treatment with Octreotide Depot for tumour control should be continued in the absence of tumour progression.

Special populations

Use in patients with impaired renal function

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 patients with impaired hepatic function

In a study with octreotide administered subcutaneously and intravenously, it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. Due to the wide therapeutic window of octreotide, no dose adjustment of Octreotide Depot is necessary in patients with liver cirrhosis.

Use in the elderly

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

Paediatric population

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

Method of administration

For instructions on reconstitution of the medicine before administration, see Section 6.6.

Following reconstitution, the suspension has a uniform milky appearance.

Octreotide Depot may only be administered by deep intramuscular injection. The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

General

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

The therapeutic benefits of a reduction in growth hormone (GH) levels and 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 (see Section 4.6).

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 octreotide treatment and may be associated with cholecystitis and biliary duct dilatation (see Section 4.8). Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients taking Sandostatin LAR in the post-marketing setting. Ultrasonic examination of the gallbladder before and at about 6 monthly intervals during Octreotide Depot therapy is recommended.

Glucose metabolism

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 subcutaneous octreotide, in some instances, a state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

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 subcutaneous administration may result in increases in post-prandial glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

In patients with insulinomas, octreotide, because of its greater relative potency in inhibiting the secretion of GH and glucagon than that of insulin, and because of the shorter duration of its inhibitory action on insulin, may increase the depth and prolong the duration of hypoglycaemia. These patients should be closely monitored.

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin 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 Octreotide Depot in patients who have a history of vitamin B_{12} deprivation.

4.5 Interaction with other medicinal products and other forms of interaction

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).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Octreotide Depot is administered concomitantly (see Section 4.4).

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

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

Limited published data indicate that somatostatin 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 (e.g. quinidine, terfenadine) should therefore be used with caution.

4.6 Fertility, pregnancy and lactation

Use in pregnancy
There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience, data on a limited number of exposed pregnancies have been reported in patients with acromegaly, however, in half of the cases the pregnancy outcomes are unknown. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100 to 300 micrograms/day of octreotide subcutaneous 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.

Studies with octreotide in laboratory animals have not shown reproductive toxicological effects of octreotide. A transient growth retardation of offspring was observed in rats, possibly consequent upon the specific endocrine profile of the species tested (see Section 5.3).

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

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.

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 5.3).

4.7 Effects on ability to drive and use machines

No data exist on the effects of Octreotide Depot on the ability to drive and use machines.

4.8 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 reactions

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

Adverse drug reactions from clinical trials (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical studies

Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence
Common:	Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces
Nervous system disorders	
Very common:	Headache
Common:	Dizziness
Endocrine disorders	
Common:	Hypothyroidism, thyroid dysfunction (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, impaired glucose tolerance, decreased appetite
Uncommon:	Dehydration
General disorders and administration site conditions	
Very common:	Injection site reactions
Common:	Asthenia
Investigations	
Common:	Elevated transaminase levels
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea
Cardiac disorders	
Common:	Bradycardia
Uncommon:	Tachycardia

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 derived from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders
Thrombocytopenia
Immune system disorders
Anaphylaxis, allergy/hypersensitivity reactions
Skin and subcutaneous tissue disorders
Urticaria
Hepatobiliary disorders
Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice
Cardiac disorders
Arrhythmias
Investigations
Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels

Description of selected adverse 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 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.

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 to 30% of long-term recipients of subcutaneous octreotide. The prevalence in the general population (aged 40 to 60 years) is about 5 to 20%. Long-term exposure to octreotide prolonged-release injection of patients with acromegaly or gastro-entero-pancreatic tumours suggests that treatment with octreotide prolonged-release injection does not increase the incidence of gallstone formation, compared with subcutaneous treatment. Ultrasonic examination of the gallbladder before and at about 6 monthly intervals during Sandostatin LAR therapy is recommended. If gallstones do

occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery (see Section 6.6).

Pancreatitis

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

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 repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see Section 4.4).

Hypersensitivity and anaphylactic reactions

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

Injection site reactions

Injection site related reactions including pain, redness, haemorrhage, pruritus, swelling or induration were commonly reported in patients receiving octreotide prolonged-release injection; however, these events did not require any clinical intervention in the majority of the cases.

Thrombocytopenia

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

Cancer patients receiving doses of Octreotide Depot up to 60 mg/month and up to 90 mg/2 weeks have been reported. These doses were in general well tolerated; however, the following adverse events have been reported: frequent urination, fatigue, depression, anxiety, and lack of concentration.

The management of overdosage is symptomatic.

For information on the management of overdose, contact the New Zealand Poison Information Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatostatin analogues, ATC code: H01CB02

Mechanism of action

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

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

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

- Release of GH stimulated by arginine, exercise- and insulin-induced hypoglycaemia,
- Post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and arginine-stimulated release of insulin and glucagon,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH).

Pharmacodynamic effects

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, Octreotide Depot, a galenical formulation of octreotide suitable for repeated administration at intervals of 4 weeks, delivers consistent and therapeutic octreotide serum concentrations thus consistently lowering GH and normalising IGF 1 serum concentrations in the majority of patients. In most patients, octreotide prolonged-release injection markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paraesthesia, fatigue, osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, octreotide prolonged-release injection was reported to lead to shrinkage of the tumour (prior to surgery). However, surgery should not be delayed.

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.

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

Glucagonomas
Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide on the state of mild diabetes mellitus which frequently occurs is not marked and, in general, does not result in a reduction of requirements for insulin or oral hypoglycaemic agents. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide 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 H2 receptor blocking agents controls the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid, such control may be incomplete. Diarrhoea may also be a prominent symptom not alleviated in all patients by this therapy. Octreotide alone or in conjunction with proton pump inhibitors or H2 receptor antagonists may reduce gastric acid hypersecretion and improve symptoms, including diarrhoea. Other symptoms possibly due to peptide production by the tumour, e.g. flushing, may also be relieved. Plasma gastrin levels fall in some patients.

Insulinomas
Administration of octreotide produces a fall in circulating immunoreactive insulin. In patients with operable tumours, octreotide may help to restore and maintain normoglycemia pre-operatively. In patients with inoperative benign or malignant tumours, glycaemic control may be improved even without concomitant sustained reduction in circulating insulin levels.

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

Clinical Efficacy and Safety

Acromegaly
Two dose finding studies (SMSC 201-E-01 and SMSC 202-E-00) were initially carried out with octreotide prolonged release injection in acromegalic patients. These studies were prospective single dose, double-blind, randomized, multi-centre studies designed to assess the following doses of octreotide prolonged release injection injected intramuscularly: 10, 20 and the 30 mg.

Patients who showed GH suppression on t.i.d. octreotide s.c. pre-treatment were selected for these studies. Out of the 93 patients included, 78 were "responders" (mean 12- hour GH serum concentrations below 5 µg/L during pre-treatment with octreotide s.c.) and 15 patients were "partial responders" to octreotide s.c. (GH mean concentrations suppressed to approximately 50% of pre-treatment levels but not to below 5 µg/L).

The primary efficacy parameter was the mean 12-hour GH serum concentrations. The results of the double-blind studies showed that the 20 and 30 mg doses of octreotide prolonged release injection are able to suppress GH levels below 5µg/L from day 14 until day 42. The i.m. injection was well tolerated locally and the adverse events analysis reflected the known gastrointestinal reactions to octreotide.

To document the long-term tolerability, safety and efficacy of octreotide prolonged release injection in acromegalic patients, three prospective open-label extensions for each of the two double-blind studies were completed (SMSC 201-E-02/-03/-04 and SMSC 202-E-01/-02/-03).

All patients that had participated to studies SMSC 201-E-01 and SMSC 202-E-00 and had well tolerated the study drug, were offered to continue treatment with additional injections of octreotide prolonged release injection in the open label extension studies. A total of 101 patients entered these studies and 87 completed all extensions, thus receiving 28 injections of octreotide prolonged release injection.

Investigators were allowed to titrate patients to their optimal therapeutic response (using 10, 20, 30 or exceptionally 40 mg doses). An interval of 28 days between injections was considered optimal for providing consistent steady-state concentrations of octreotide, based on pharmacokinetic simulation of single dose profiles and considering the linearity of pharmacokinetics of octreotide. The primary efficacy endpoint in the extension studies was the 8-hours GH serum concentrations.

These extension studies demonstrated that long-term treatment of acromegalic patients with octreotide prolonged release injection administered at doses of 10-30 mg i.m. in patients known to be responsive to octreotide s.c. results in a sustained suppression of mean 8-hour GH levels throughout the dosing interval. These effects were accompanied by a marked reduction in IGF-I concentrations and a persistent regression of the symptoms of acromegaly.

Long-term systemic tolerability of octreotide prolonged release injection was good, the pattern, severity and duration of adverse events was similar to those historically reported for the s.c. treatment with octreotide and for short-term treatment with octreotide prolonged release injection.

GEP tumours

The clinical trial program for octreotide prolonged release injection in GEP tumours consisted of one controlled clinical study (SMSE 351) which was carried out in patients with malignant carcinoid syndrome symptomatically controlled by octreotide s.c..

Study SMSE 351 was a randomised, double-blind, multicenter prospective study of efficacy, safety and tolerability of multiple dose levels of octreotide prolonged release injection (10, 20 and 30 mg doses) administered at 4-week intervals versus open-label subcutaneous octreotide. Ninety-three patients were enrolled and 80 completed the study.

Assessment of treatment success, partial treatment success or treatment failure was based on the degree and duration of suppression of carcinoid symptoms as indicated by the need for rescue therapy with octreotide in patients randomised to one of the octreotide prolonged release injection groups, or by the need for an increase in dosage in patients randomized to the octreotide group, at the end of Week 20 and Week 24.

A level of efficacy comparable to that achieved with octreotide s.c. was observed with octreotide prolonged release injection after the 5th and 6th injections at Weeks 20 and 24 respectively, and at endpoint (see table 3).

Table 3: Summary of treatment success in Study SMSE 351 (Intent To Treat population)

Visit	Treatment Outcome	Octreotide s.c. n (%)	Octreotide prolonged release injection 10 mg n (%)	Octreotide prolonged release injection 20 mg n (%)	Octreotide prolonged release injection 30 mg n (%)
Week 20	n	26	19	16	23
	Success	16 (61.5)	12 (63.2)	10 (62.5)	14 (60.9)
	Part. Success	1 (3.8)	2 (10.5)	1 (6.3)	-
Week 24	n	26	19	15	21
	Success	14 (53.8)	12 (63.2)	9 (60.0)	13 (61.9)
	Part. Success	1 (3.8)	-	1 (6.7)	1 (4.8)
Endpoint	n	26	22	20	25
	Success	14 (53.8)	12 (54.5)	9 (45.0)	13 (52.0)

Part. Success	1 (3.8)	-	1 (5.0)	1 (4.0)

Success = no need for rescue octreotide s.c or increased s.c dosage
Part. Success = need for rescue octreotide s.c or increased s.c dosage on no more than 2 occasions during the preceding 4 weeks for a total of 5 days or less.
Endpoint = last not missing post-baseline evaluation

The data recorded in Study SMSE 351 showed that octreotide prolonged release injection is as effective and as well tolerated as octreotide s.c. injections in the treatment of patients with carcinoid symptoms.

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 prolonged-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 the secondary endpoint overall survival, as the median overall survival was not reached at the time of interim analysis in the Sandostatin LAR group.

85 patients were randomised to receive octreotide prolonged-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 tumours/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.

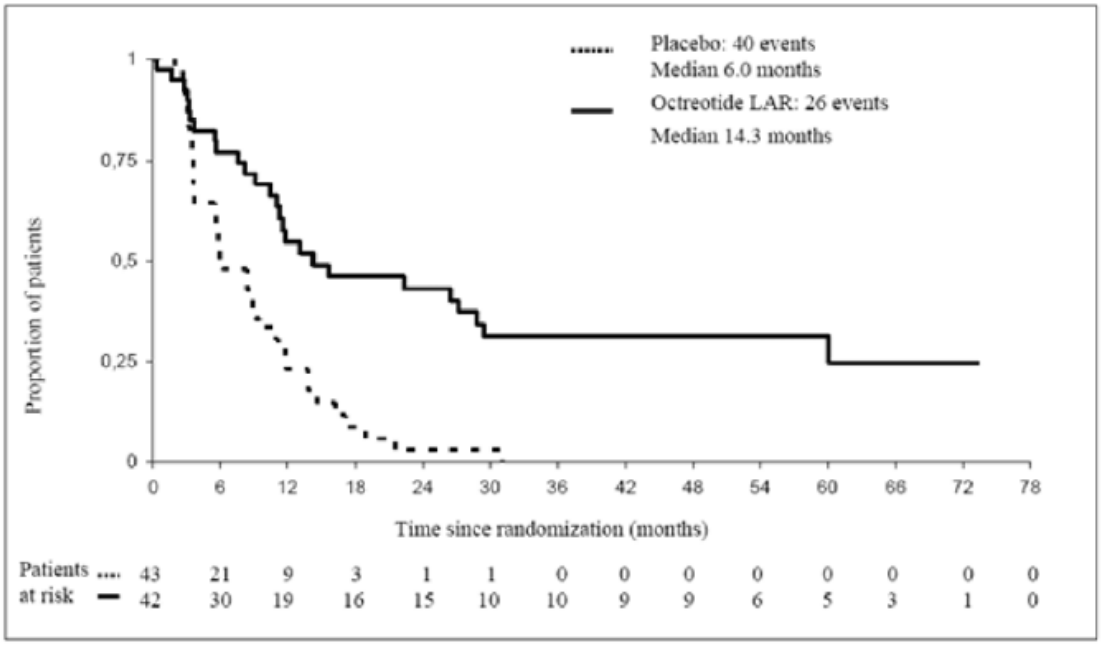
The primary endpoint was time to tumour progression or tumour-related death (TTP).

In the intent-to-treat analysis population (ITT) (all randomised patients), 26 and 41 progressions or tumour-related deaths were seen in the octreotide prolonged-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 randomization, 26 and 40 progressions or tumour-related deaths were observed in the octreotide prolonged-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 prolonged-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 prolonged-release injection and placebo recipients, respectively (HR = 0.24; 95% CI, 0.13 to 0.45; p-value =0.0000036).

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



Logrank test stratified by functional activity: P=0.000072, HR= 0.34 [95%-CI: 0.20–0.59]

Table 4; TTP results by analysis populations

	TTP Events		**Median TPP months [95% C.I.]**		**HR [95% C.I.]**
	octreotide prolonged-release injection	**Placebo**	**octreotide prolonged-release injection**	**Placebo**	**p-value***
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

Subgroup analyses on the per-protocol analysis population demonstrated that treatment effect was similar in patients with functionally active (HR = 0.23; 95% CI, 0.09 to 0.57) and 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 prolonged-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 prolonged-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 Sandostatin LAR. 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 Sandostatin LAR 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 prolonged-release injection in this trial was consistent with its established safety profile.

5.2 Pharmacokinetic properties

Absorption

After single i.m. injections of octreotide prolonged-release injection, the serum octreotide concentration reaches a transient initial peak within 1 hour after administration, followed by a progressive decrease to a low undetectable octreotide level within 24 hours. After this initial peak on day 1, octreotide remains at sub-therapeutic levels in the majority of the patients for the following 7 days. Thereafter, octreotide concentrations increase again, and reach plateau concentrations around day 14 and remain relatively constant during the following 3 to 4 weeks. The peak level during day 1 is lower than levels during the plateau phase and no more than 0.5% of the total drug release occurs during day 1. After about day 42, the octreotide concentration decreases slowly, concomitant with the terminal degradation phase of the polymer matrix of the dosage form.

In patients with acromegaly, plateau octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg octreotide prolonged-release injection amount to 358 ng/L, 926 ng/L, and 1,710 ng/L, respectively. Steady-state octreotide serum concentrations, reached after 3 injections at 4 week intervals, are higher by a factor of approximately 1.6 to 1.8 and amount to 1,557 ng/L and 2,384 ng/L after multiple injections of 20 mg and 30 mg octreotide prolonged-release injection, respectively.

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 prolonged-release injection given at 4 week intervals also increased linearly with dose and were 1,231 (894) ng/L, 2,620 (2,270) ng/L and 3,928 (3,010) ng/L, respectively.

No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a duration of up to 28 monthly injections of octreotide prolonged-release injection.

Distribution and Biotransformation

The pharmacokinetic profile of octreotide after injection of octreotide prolonged-release injection reflects the release profile from the polymer matrix and its biodegradation. Once released into the systemic circulation, octreotide distributes according to its known pharmacokinetic properties, as described for subcutaneous administration. The volume of distribution of octreotide at steady-state is 0.27 L/kg and the total body clearance is 160 mL/min. Plasma protein binding amounts to 65% and essentially no drug is bound to blood cells.

Steady-state trough octreotide concentrations were not correlated with age and BMI, but moderately correlated with body weight (52.3–133 kg) and was significantly different between male and female patients, i.e. about 17% higher for female patients.

5.3 Preclinical safety data

Repeat dose toxicity

In two repeat dose studies performed in rats by i.m. injection of 2.5 mg Sandostatin LAR in 50 mg microspheres every 4 weeks for 21/24 weeks, no drug-related necropsy findings were observed. The only histopathological findings considered to be of significance were at the injection site in treated and control animals, where the microspheres had provoked a reversible granulomatous myositis.

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. The microspheres were devoid of mutagenic potential when tested in standard assays for genotoxicity.

Carcinogenicity/chronic toxicity

In studies in rats in which s.c. Sandostatin at daily doses up to 1.25 mg/kg body weight were administered, fibrosarcomas were observed, predominantly in a number of male animals, at the s.c. injection site after 52, 104 and 113/116 weeks. Local tumours occurred also in the control rats, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were observed neither in mice receiving daily s.c. injections of Sandostatin at doses up to 2 mg/kg for 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. Sandostatin also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest s.c. dose level of 1.25 mg/kg per day. The 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 tumours in rats are species-specific and are not relevant for the use of the drug in humans.

Reproduction toxicity

Reproduction studies have been performed with Sandostatin 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 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/foetal or other reproduction effects due to octreotide.

The microspheres were devoid of reproductive toxicological effects when tested in standard studies for reproductive toxicity in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder (Vial):
Poly (DL-lactide-co-glycolide)
Mannitol (E421)

Diluent (Prefilled syringe):
Carmellose sodium
Mannitol (E421)
Poloxamer
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

After reconstitution, use immediately.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Octreotide Depot may be stored below 25°C on the day of injection.

For storage conditions after reconstitution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

Octreotide Depot 10 mg: Each unit contains one glass vial with rubber stopper (chlorobutyl rubber), sealed with an aluminium cap with a dark blue coloured flip-off seal, containing powder for suspension for injection and one pre-filled glass syringe with tip cap and plunger stopper (bromobutyl rubber) with 2 mL of diluent, co-packaged in a plastic tray with one vial adapter and one safety injection needle.

Octreotide Depot 20 mg: Each unit contains one glass vial with rubber stopper (chlorobutyl rubber), sealed with an aluminium cap with an orange coloured flip-off seal, containing powder for suspension for injection and one pre-filled glass syringe with tip cap and plunger stopper (bromobutyl rubber) with 2 mL of diluent, co-packaged in a plastic tray with one vial adapter and one safety injection needle.

Octreotide Depot 30 mg: Each unit contains one glass vial with rubber stopper (chlorobutyl rubber), sealed with an aluminium cap with a red granate coloured flip-off seal, containing powder for suspension for injection and one pre-filled glass syringe with tip cap and plunger stopper (bromobutyl

rubber) with 2 mL of diluent, co-packaged in a plastic tray with one vial adapter and one safety injection needle.

Pack size: One unit.

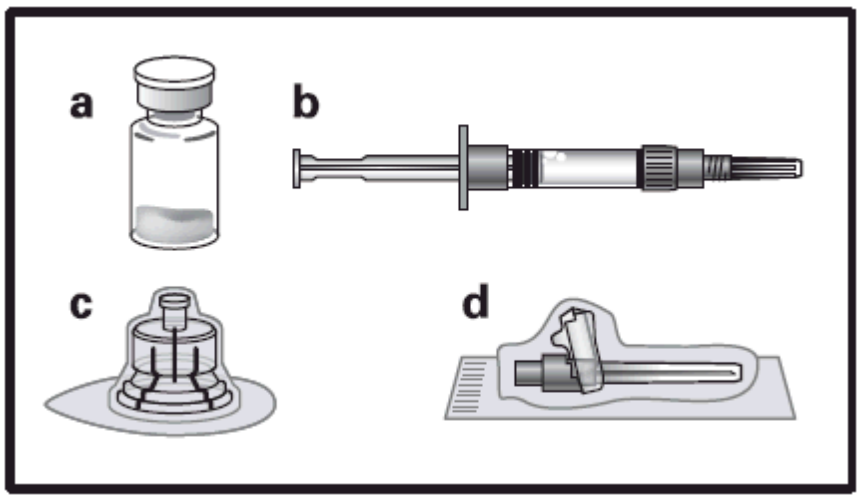
6.6 Special precautions for disposal and other handling

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

Instructions for preparation and intramuscular injection for Octreotide Depot

FOR DEEP INTRAMUSCULAR INJECTION ONLY

Included in the injection kit:



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

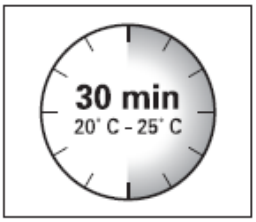
d. One safety injection needle.

Follow the instructions below carefully to ensure proper reconstitution of Octreotide Depot before deep intramuscular 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 healthcare professional.



Step 1

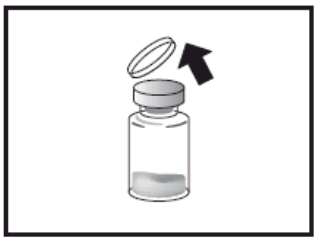
Remove the Octreotide Depot injection kit from refrigerated storage.

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.

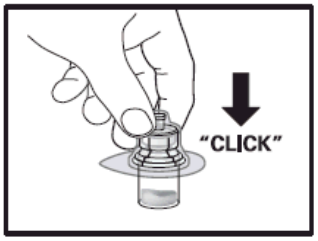
Step 2

Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe.

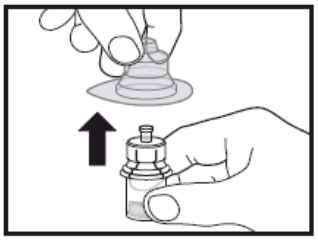


Remove the lid film of the vial adapter packaging, but do NOT remove the vial adapter from its packaging.

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”.

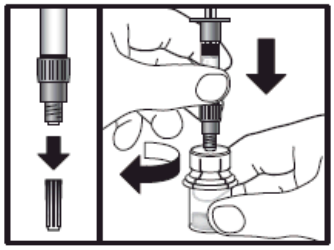


Lift the packaging off the vial adapter with a vertical movement.

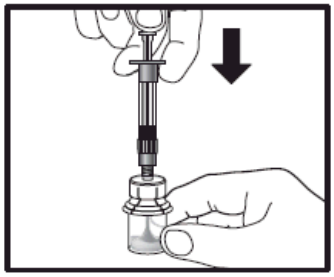


Step 3

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.

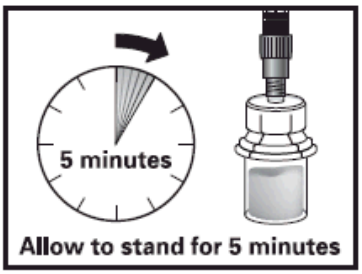


Step 4

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.

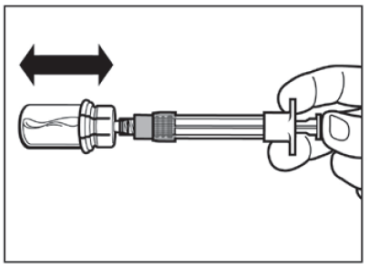
At this stage prepare the patient for injection.



Step 5

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

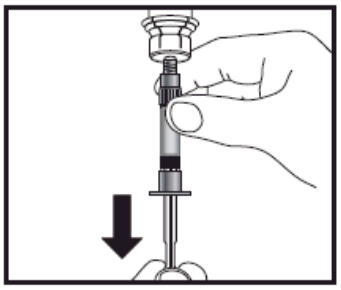
ATTENTION: Keep the plunger pressed and shake the vial moderately in a horizontal direction for a minimum of 30 seconds so that the powder is completely suspended (milky uniform suspension). Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.

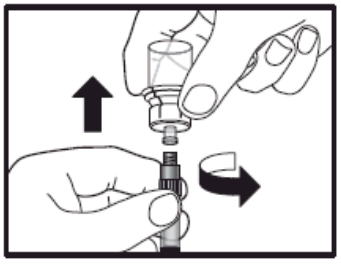


Step 6

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.

If immediate administration is delayed, gently re-shake the syringe to ensure a milky uniform suspension.

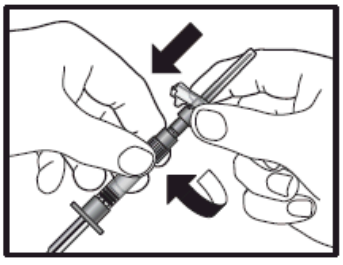
Prepare injection site with an alcohol wipe.

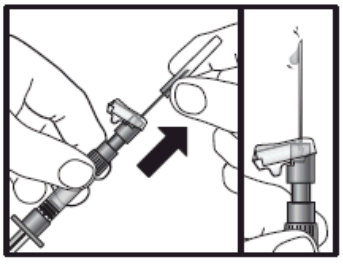
Pull the protective cover straight off the needle.

Gently tap the syringe to remove any visible bubbles and expel them from the syringe.

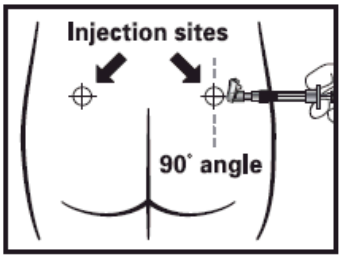
Proceed **immediately** to **Step 8** for administration to the patient.

Any delay may result in sedimentation.





Step 8



Octreotide Depot must be given only by deep intramuscular injection, **NEVER** intravenously.

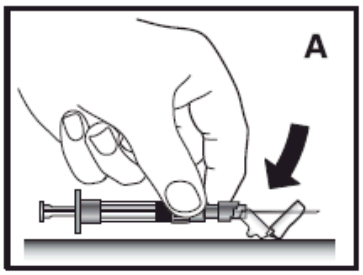
Insert the needle fully into the left or right gluteus at a 90° angle to the skin.

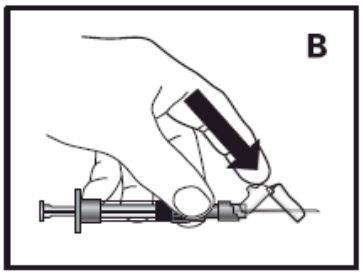
Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated).

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 two 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.

Record injection site on patient's record and **alternate monthly.**

Dispose of syringe immediately (in a sharps container).

<u>Recommendation for the management of patients during Octreotide Depot treatment with respect to the development of gallstones</u>

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 Octreotide Depot treatment.
3. If stones are already present before the start of therapy, the potential benefit of Octreotide Depot should be assessed against the potential risks associated with the gallstones. There is no evidence at present that Octreotide Depot adversely affects the course or prognosis of pre-existing gallstones.
4. Management of patients who develop gallstones in association with Octreotide Depot:
    i. Asymptomatic gallstones
    Octreotide Depot 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
Octreotide Depot 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 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Auckland, New Zealand
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

20 February 2020

10. DATE OF REVISION OF THE TEXT

28 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Minor editorial changes to text.
4.4	Gallbladder and related events: Addition of post-marketing cases of cholangitis.
4.8	Alignment of information on metabolism and nutritional disorders (change from anorexia to decreased appetite). Information clarified relating to adverse drug reactions from spontaneous reports and literature cases (frequency not known).
5.1	Minor updates to sentence formatting particularly for the section on information regarding Gastrinomas/Zollinger-Ellison syndrome. Study number identifiers included. Information on PROMID study updated.
5.3	Information updated regarding repeat dose toxicity, genotoxicity, carcinogenicity/chronic toxicity and reproduction toxicity.
6.3	Shelf life updated to 3 years