NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Octreotide 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL vial of DBL Octreotide solution for injection contains 0.05 mg, 0.1 mg or 0.5 mg of octreotide as octreotide acetate.

Excipients with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL Octreotide is a clear colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

For the relief of symptoms associated with functional gastro-entero-pancreatic (GEP) endocrine tumours:

- Carcinoid tumours with features of the carcinoid syndrome
- Vasoactive intestinal peptide secreting tumours (VIPomas)
- Glucagonomas
- Gastrinomas/Zollinger-Ellis syndrome, usually in conjunction with proton pump inhibitors, or H2-antagonist therapy
- Insulinomas, for pre-operative control of hypoglycaemia and for maintenance therapy
- GRFomas.

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

For prevention of complications following pancreatic surgery.

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

4.2 Dose and method of administration

Dose

Acromegaly

Initially 0.05 to 0.1 mg by subcutaneous injection every 8 or 12 hours. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH <2.5 ng/mL; IGF-1 within normal range) and clinical symptoms and on tolerability. In most patients, the optimal daily dose will be 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of GH and IGF-1 should be made every 6 months.

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

Gastro-entero-pancreatic endocrine tumours

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

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

Complications following pancreatic surgery

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

Bleeding gastro-oesophageal varices

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

In cirrhotic patients with bleeding gastro-oesophageal varices, octreotide has been well tolerated at continuous i.v. doses of up to 50 micrograms/hour for 5 days.

Special populations

Elderly population

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

Renal impairment

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

Hepatic impairment

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

Paediatric population

Experience with octreotide in children is very limited.

Method of administration

DBL Octreotide may be administered directly by subcutaneous (s.c.) injection or by intravenous (i.v.) infusion after dilution. For instructions on dilution of the medicinal product before infusion, refer to section 6.6.

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

To reduce local discomfort, it is recommended that the solution reaches room temperature before injection. Multiple injections at short intervals at the same site should be avoided. Vials should be opened just prior to administration and any unused portion discarded.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Do not use if particulates and/or discolouration are observed. DBL Octreotide contains no antimicrobial agent. Product is for single use in one patient only. Discard any remaining contents.

4.3 Contraindications

Hypersensitivity to octreotide or to any component of the formulation.

4.4 Special warnings and precautions for use

Pancreatic function

Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastro-entero-pancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating, and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

Cardiovascular related events

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

Development of gallstones

Cholelithiasis is a very common event during octreotide treatment and may be associated with cholecystitis and biliary duct dilatation (see section 4.8). Additionally, in the post-marketing setting, cases of cholangitis have been reported as a complication of cholethiasis in patients receiving octreotide. Ultrasonic examination of the gallbladder before, and at about 6 to 12 month intervals during octreotide therapy is therefore recommended.

GH secreting pituitary tumours

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

Gastro-entero-pancreatic endocrine tumours

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

Effects on glucose regulation

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

In patients with insulinomas, octreotide, because of its greater relative potency in inhibiting the secretion of GH and glucagon than that of insulin, and because of the shorter duration of its inhibitory action on insulin, may increase the depth and prolong the duration of hypoglycaemia. These patients should be closely monitored during initiation of octreotide therapy and at each change of dosage. Marked fluctuations of blood glucose concentration may possibly be reduced by smaller, more frequently administered doses.

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

Oesophageal varices

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

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

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

Thyroid function

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

Effects on laboratory tests

See Nutrition above.

4.5 Interaction with other medicines and other forms of interaction

Octreotide has been reported 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 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, terfenadine) should therefore be used with caution.

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

The therapeutic benefits of a reduction in 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.

Pregnancy

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

100-300 micrograms/day of octreotide subcutaneously. 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.

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

Breast-feeding

It is unknown whether octreotide is transferred into in human breast milk. Animal studies have shown transfer 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. Fertility as well as pre-, peri- and post-natal studies in female rats revealed no adverse effects on reproductive performance and development of the offspring, when subcutaneous doses of up to 1 mg/kg body weight per day were administered. Some retardation of the physiological growth noted in pups was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity.

4.7 Effects on ability to drive and use machinery

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 Undesirable effects

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.

Adverse drug reactions accumulated from clinical studies with octreotide (see Table 1) are listed by the MedDRA system organ class (SOC). Within each SOC, the adverse drug reactions are ranked by frequency, with the most frequent first, using the following convention: *very common (≥ 1/10); common (≥ 1/100, < 1/10)*; *uncommon (≥ 1/1,000, <1/100)*; *rare (≥ 1/10,000, <1/1,000)*; *very rare (< 1/10,000)*, including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse drug reactions reported in clinical studies

Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence.
Common:	Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces.
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, impaired glucose tolerance, 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 disorders	
Common:	Dyspnoea.
Cardiac disorders	
Common:	Bradycardia.
Uncommon:	Tachycardia.

* Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with octreotide, in some instances, a state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported. Flushing and oedema, events attributable to the underlying conditions, have been observed.

Description of selected adverse drug reactions

Gastrointestinal disorders and nutrition

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

Although measured faecal fat may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption.

Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of DBL Octreotide administration, that is, by injecting before meals or on retiring to bed.

Gallbladder and related reactions

Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Development of gallstones has been reported in 15-30% of long-term recipients of octreotide. The prevalence in the general population (aged 40 to 60 years) is estimated from reviews to be about 5-20%. The presence of gallstones or biliary sludge in octreotide-treated patients is largely asymptomatic. Symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Injection site reactions

Local reactions may occur and include pain, a sensation of stinging, tingling or burning at the site of injection, with redness, swelling, irritation and rash, rarely lasting more than 15 minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection, or by injecting a smaller volume using a more concentrated solution.

Pancreatitis

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

Cardiac disorders

Bradycardia is a common adverse reaction with somastatin analogues. In both acromegalic and carcinoid syndrome patients, arrhythmia and ECG changes such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes were observed. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see section 4.4).

Post-marketing experience

Spontaneously reported adverse reactions, presented in Table 2, are reported voluntarily and it is not always possibly to reliably establish frequency or a casual relationship to drug exposure.

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

Blood and lymphatic system disorders Thrombocytopenia.
Immune 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.

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

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

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.

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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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) over a period of 1-2 weeks or 3,000 micrograms/day (1,000 micrograms three times a day) for 2 days administered subcutaneously. Some of the adverse events reported included arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving higher doses of continuous infusion (100 micrograms/hour) and/or bolus of octreotide intravenously (50 microgram bolus followed by 50 micrograms/hour continuous infusion).

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

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

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02.

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

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

In healthy subjects octreotide has been shown to inhibit:

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

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

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

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

Octreotide's effects in the different tumour types 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.
- 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-Ellis 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 by this therapy. Octreotide alone or in conjunction with proton pump inhibitors or H_2-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, which may, however, be of short duration (about 2 hours). In patients with operable tumours, octreotide may help to restore and maintain normoglycaemia pre-operatively. In patients with inoperable benign or malignant tumours, glycaemic control may be improved 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 resultant acromegaly. This is probably due to inhibition of GRF and GH secretion, and a reduction in pituitary enlargement may follow.

Complications following pancreatic surgery

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

Bleeding gastro-oesophageal varices

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

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, octreotide is rapidly and completely absorbed. Peak plasma concentrations are reached within 30 minutes.

Distribution

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

Elimination

The elimination half-life after subcutaneous administration is 100 minutes. Most of the peptide is eliminated via the faeces, while approximately 32% is excreted unchanged into the urine.

Effect of renal and hepatic dysfunction on pharmacokinetics

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

The elimination capacity may be reduced in patients with liver cirrhosis (see section 4.4), but not in patients with fatty liver disease.

5.3 Preclinical safety data

Carcinogenicity

In rats receiving octreotide acetate at daily doses up to 1.25 mg/kg body weight, fibrosarcomas were observed, predominantly in a number of male animals, at the subcutaneous 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 not observed either in mice receiving daily subcutaneous injections of octreotide at doses up to 2 mg/kg for 98 weeks, or in dogs which were treated with daily subcutaneous doses of the drug for 52 weeks. There have been no reports of tumour formation at the injection sites in patients treated for up to 15 years with 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 carcinogenicity study in rats with subcutaneous octreotide also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest subcutaneous 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-medicated tumours in rats are species specific and are not relevant for the use of the drug in humans.

Mutagenicity

Octreotide and/or its metabolites were devoid of mutagenic potential when investigated *in vitro* in validated bacterial and mammalian cell test systems. Increased frequencies of chromosomal changes were observed in V79 Chinese hamster cells in vitro, albeit at high and cytotoxic concentrations only. Chromosomal aberrations were however not increased in human lymphocytes incubated with octreotide acetate in vitro. *In vivo*, no clastogenic activity was

observed in the bone marrow of mice treated with octreotide intravenous (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 a validated *in vitro* bacterial assay.

Reproductive toxicity

Reproduction studies in rats and rabbits revealed no evidence of teratogenic, embryo/fetal or other reproduction effects due to octreotide at parental doses of up to 1 mg/kg/day. Some retardation of physiological growth was noted in the offspring of rats which was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity.

Local site reactions

In a 52-week toxicity study in rats, predominantly in males, sarcomas were noted at the subcutaneous injection site only at the highest dose (about 8 times the maximum human dose based on body surface area). No hyperplastic or neoplastic lesions occurred 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 with octreotide for up to 15 years. All the information available at present indicates that the findings in rats are species specific and have no significance for the use of the drug in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

The product should be used immediately after opening.

Diluted solutions should be used immediately after preparation.

6.4 Special precautions for storage

Store between 2°C and 8°C (Refrigerate. Do not freeze).

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

For storage conditions after dilution, refer to section 6.6.

DBL Octreotide must be kept out of the reach and sight of children.

6.5 Nature and contents of container

DBL Octreotide Injection is available as:

0.05 mg/1 mL glass vial, 5 pack

0.1 mg/1 mL glass vial, 5 pack

0.5 mg/1 mL glass vial, 5 pack

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

Prior to administration the solution should be inspected visually for changes of colour or solid particles.

The diluted solutions of DBL Octreotide (octreotide acetate) in 0.9% sodium chloride solution for injection and stored in PVC bags or in polypropylene syringes are physically and chemically stable for 7 days when stored at below 25°C. From a microbiological point of view, the diluted solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the user and normally should not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Before administration the solution has to be brought to room temperature again.

When DBL Octreotide is to be administered as intravenous infusion, the contents of one vial should normally be dissolved in 60 mL physiological saline, and the resulting solution should be infused by means of an infusion pump. This should be repeated as often as necessary until the prescribed duration of treatment is reached. DBL Octreotide has also been infused in lower concentrations.

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

6.7 Physicochemical properties

DBL Octreotide Injection contains octreotide acetate, a synthetic octapeptide analogue of Somatostatin.

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-L-threoninol.

CAS number: 79517-01-4 (octreotide acetate).

MW: 1019.3 (free peptide).

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

21 September 2006

10. DATE OF REVISION OF THE TEXT

21 August 2024

Summary table of changes

Section changed	Summary of new information
Throughout	Minor editorial changes
4.4	Safety update for pancreatic function
4.8	Update to ADR reporting website