NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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 ampoule of Octreotide injection contains 0.05 mg, 0.1 mg or 0.5 mg of octreotide (as acetate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Octreotide injection is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For symptomatic control and reduction of 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 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 for 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 limited.

Method of administration

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

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

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

General

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 (see section 4.6).

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

Cardiovascular related events

Uncommon cases of bradycardia have been reported. 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

The incidence of gallstone formation with octreotide treatment is estimated to be between 15 to 30%. The incidence in the general population is 5 to 20%. Ultrasonic examination of the gallbladder before, and at about 6 to 12 month intervals during octreotide therapy is therefore recommended. The presence of gallstones in octreotide-treated patients is largely

asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Guidelines for the management of patients during octreotide treatment with respect to the development of gallstones

1. Patients should undergo a baseline ultrasound examination of the gallbladder prior to commencing octreotide.
2. Periodic repeat ultrasound examination of the gallbladder should be performed, preferably at about 6 to 12 month intervals, through octreotide treatment.
3. If stones are already present before the start of therapy, the potential benefit of octreotide should be assessed against the potential risks associated with the gallstones. There is no evidence at present that octreotide adversely affects the course or prognosis of pre-existing gallstones.
4. Management of patients who develop gallstones in association with octreotide:

Asymptomatic gallstones

Octreotide may be either stopped or 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.

Symptomatic gallstones

Octreotide 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 includes combined bile acid therapy (e.g. chenodeoxycholic acid [CDCA] 7.5 mg/kg per day together with ursodeoxycholic acid [UDCA] 7.5 mg/kg per day) associated with ultrasound monitoring until the stones have completely disappeared.

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, the 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 prandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

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.

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 dose.

Elderly population

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

Paediatric population

Experience with octreotide in children is limited.

4.5 Interaction with other medicines and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

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 100-300 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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development apart from some transient retardation of physiological growth (see section 5.3).

Octreotide should only be prescribed to pregnant women under compelling circumstances (see section 4.4).

Australian categorisation definition of Category C:

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Breast-feeding

It is unknown whether 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

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

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

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.

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

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

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 octreotide subscutaneous administration, that is, by injecting before meals or on retiring to bed.

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.

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).

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

Adverse drug reactions (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, anorexia.
Uncommon:	Dehydration.
General disorders and administration site	
Very common:	Injection site localized pain.
Investigations	
Common:	Elevated transaminase levels.
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
Respiratory disorders	
Common:	Dyspnoea.
Cardiac disorders	
Common:	Bradycardia.
Uncommon:	Tachycardia.

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 causal relationship to drug exposure.

Table 2 Adverse drug reactions derived from spontaneous reports

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.

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 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, hepatomegaly, and lactic acidosis.

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.

Treatment

The management of overdosage is symptomatic.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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)

Pharmacotherapeutic group: Antigrowth hormone (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 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
- Postprandial release of insulin, glucagon, gastrin, other peptides of the gastro-entero-pancreatic (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 flush 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 H_2-receptor blocking agents controls the recurrent peptic ulceration which results from chronic gastrin-stimulated hypersecretion of gastric acid, such control may be incomplete. 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. flush, 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.

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

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).

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

Genotoxicity

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.

Carcinogenicity

In rats receiving octreotide acetate at daily does up to 1.25mg/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 observed neither in mice receiving daily subcutaneous injections of octreotide at doses up to 2mg/kg for 98 weeks, nor in dogs which were treated with daily subcutaneous doses of the drug for 52 weeks.

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.

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. 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 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.

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.

Acute toxicity

Acute toxicity studies of octreotide in mice revealed LD_{50} values of 72 mg/kg by the intravenous route and of 470 mg/kg by the subcutaneous route. The acute intravenous LD_{50} value of octreotide in rats was determined at 18mg/kg. Octrotide acetate was well tolerated by dogs receiving up to 1 mg/kg body weight by intravenous bolus injection.

Repeat-dose toxicity

A 26-week intravenous toxicity study in dogs carried out at dose levels of up to 0.5 mg/kg twice per day revealed progressive changes in acidophil prolactin-containing cells in the pituitary. Further investigations showed this to be within physiological range, apparently without relationship to the exogenously administered somatostatin. There were no significant alterations in plasma hormone levels. Female Rhesus monkeys receiving the same dose level of 0.5 mg/kg b.i.d. for 3 weeks failed to reveal pituitary changes, and there were no alterations of basal levels of plasma growth hormone, prolactin, or glucose.

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

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 40 times the maximum human dose). 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

Glycine, mannitol, hydrochloric acid, water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at 2° to 8°C (refrigerate, do not freeze) protect from light.

The unopened product may be stored for up to two weeks at or below 25°C.

Ampoules stored unrefrigerated for longer than two weeks must be discarded.

The product should be used on one occasion in one patient only.

Once the ampoule is opened, any unused remainder should be discarded immediately.

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

6.5 Nature and contents of container

Octreotide injection is available as:

- 0.05 mg/1 mL glass ampoule, 5 pack
- 0.1 mg/1 mL glass ampoule, 5 pack
- 0.5 mg/1 mL glass ampoule, 5 pack

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Max Health Ltd

PO Box 65 231, Mairangi Bay, Auckland 0754

Ph:(09) 815 2664.

9. DATE OF FIRST APPROVAL

17 November 2011

10. DATE OF REVISION OF THE TEXT

09 March 2020

Summary table of changes

Date of revision	Section changed	Summary of new information
18 Sep 2017	All	Updated to align with current NZ source document Updated to SPC format.
09 March 2020	All Section 1	Updated to align with current source document Product name changed from Octreotide MaxRx Injection to Octreotide.