AUSTRALIAN PRODUCT INFORMATION – DBL™ OCTREOTIDE INJECTION (Octreotide acetate) Solution for Injection

1. NAME OF THE MEDICINE

Octreotide acetate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

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

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

3. PHARMACEUTICAL FORM

Solution for injection.

DBL™ Octreotide Injection is a clear colourless solution free of foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system:

    - Carcinoid tumours with features of the carcinoid syndrome

    - Vasoactive intestinal peptide secreting tumours (VIPomas).

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

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

4.2 Dose and Method of Administration

Dosage

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 on clinical symptoms and on tolerability. In most patients the optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with 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, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 µg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

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

Method of Administration

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

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

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

Development of gallstones has been reported in 15 to 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 to 20%. Cholelithiasis is a very common event during octreotide treatment and may be associated with cholecystitis and biliary tract dilatation (see Section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the post-marketing setting, cases of cholangitis have been reported as a complication of cholelithiasis in patients receiving octreotide. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

GH secreting pituitary tumours

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

Gastro-entero-pancreatic endocrine tumours

In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Effects on glucose regulation

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

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

Oesophageal varices

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

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving ocreotide therapy. Monitoring of vitamin B_{12} levels is recommended during

therapy with DBL™ Octreotide Injection in patients who have a history of vitamin B_{12} deprivation.

Thyroid function

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

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

Paediatric use

Experience with octreotide in children is very limited.

Effects on laboratory tests

See subheading Nutrition above.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

Octreotide has been reported to produce a reduction in the intestinal absorption of ciclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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, such as insulin, affecting glucose metabolism may be required following initiation of octreotide therapy in patients with diabetes (see Section 4.4 Special Warnings and Precautions for Use: Effects on glucose regulation).

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

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.

Effects on fertility

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

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.

No adequate and well controlled studies have been performed 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 µg/day of subcutaneous octreotide. 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 Injection should only be prescribed to pregnant women under compelling circumstances.

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

Use in lactation

It is not known whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during treatment with DBL™ Octreotide Injection.

4.7 Effects on Ability to Drive and Use Machines

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

However, adverse effects of this medicine include dizziness and asthenia which could affect the ability to drive or operate machinery (see Section 4.8 Adverse Effects (Undesirable Effects)).

4.8 Adverse Effects (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, flatulaence, 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: Common:	Injection site reactions. Asthenia.
Investigations	
Common:	Elevated transaminase levels.
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
Respiratory disorders	
Common:	Dyspnoea.
Cardiac disorders	
Common: Uncommon:	Bradycardia. Tachycardia.

* Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation and impair post-prandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been reported.

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

Post-marketing experience

Adverse drug reactions derived from post-marketing experience with octreotide via spontaneous case reports and literature cases are presented in Table 2. Because these reactions are reported voluntarily from a population of uncertain size it is not possible to reliably estimate frequency. Adverse drug reactions are listed according to SOCs in MedDRA, and are ranked in order of decreasing seriousness within each SOC.

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

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

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

One case of clinical hypothyroidism has been reported in a patient who had received 1500 µg octreotide daily for 19 months.

Description of selected adverse drug reactions

Injection site reactions

Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness, swelling, irritation and rash. They rarely last more than fifteen 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.

Gastrointestinal system

Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder

Prolonged use of octreotide may result in gallstone formation (see Section 4.4 Special Warnings and Precautions for Use).

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 Special Warnings and Precautions for Use).

Pancreatitis

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

Reporting suspected adverse effects

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

4.9 Overdose

No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

The management of overdosage is symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). In New Zealand, call 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

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

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

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

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

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

Effects of octreotide in the different tumour types are as follows:

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

- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 µg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 µg and with multiple doses of 200 µg t.i.d. (600 µg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 µg/day as compared to 150 µg/day. The relative decrease in clearance with doses above 600 µg/day is not defined.

Distribution

The distribution of octreotide from plasma was rapid ($t_{½\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

Excretion

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

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

Effect of renal and hepatic dysfunction on pharmacokinetics:

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

5.3 Preclinical Safety Data

Genotoxicity

Carcinogenicity

In repeat dose toxicity studies in rats of 52 weeks duration and longer, predominantly in males, sarcomas were noted at the subcutaneous injection site of octreotide in an acidic vehicle and at a lower incidence with the acidic vehicle alone. These did not occur in a mouse carcinogenicity study, nor did hyperplastic or neoplastic lesions occur at the subcutaneous injection site in a 52 week dog toxicity study.

There have been no reports of tumour formation at the injection sites in patients treated for up to 15 years with octreotide. All information available at present indicates that the finding of injection site sarcomas in rats is species-specific and has no significance for the use of the drug in humans.

The 116 week rat carcinogenicity study also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest dose of 1.25 mg/kg per day. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumours were associated with estrogen dominance in the aged female rats which does not occur in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special Precautions for Storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in the original packaging in order to protect from light.

6.5 Nature and Contents of Container

DBL™ Octreotide Injection is available in glass (Type 1 coloured) vials; pack sizes:

0.05 mg/1 mL vial, 5 pack	AUST R 120734
0.1 mg/1 mL vial, 5 pack	AUST R 120735
0.5 mg/1 mL vial, 5 pack	AUST R 120736

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

Chemical structure

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

MW: 1019.3 (free peptide).

CAS number

Octreotide acetate: 79517-01-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number : 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

20 June 2008

10. DATE OF REVISION

22 March 2021

Summary table of changes

Section changed	Summary of new information
All	PI reformat/editorial changes
Section 2	Added excipients with known effect.
Section 4.2	Removed duplicated information on the use in the elderly and in children.
Section 4.4	Added information on cardiovascular related events, nutrition and thyroid function. Updated information on gallstones.
Section 4.6	Added information in relation to women of childbearing potential. Added a statement regarding the effect of octreotide on human fertility. Expanded information on the use in pregnancy.
Section 4.8	The most frequent adverse reactions are updated. Added a statement of the most common adverse reactions reported from clinical trials. Added a table of ADRs reported from clinical trials with octreotide ranked by frequency within the MedDRA SOC. ADRs derived from post-marketing experience are listed according to SOCs in MedDRA, ranked in order of decreasing seriousness within each SOC. Newly listed ADRs: dyspnoea, tachycardia, endocrine disorders, dehydration, elevated transaminase levels, arrhythmias, Blood alkaline phosphatase increased, gamma glutamyl transferase increased. Added information on cardiac disorders.
Section 5.1	Added pharmacotherapeutic group.
Section 6.4	Added recommendation to store in the original packaging in order to protect from light.

DBL™ Octreotide Injection

Octreotide (ok-tree-oh-tide) acetate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about DBL Octreotide Injection. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you using DBL Octreotide Injection against the benefits they expect it will have for you.

If you have any concerns about using this medicine, ask your doctor or pharmacist.

Keep this leaflet.

You may need to read it again.

What DBL Octreotide Injection is used for

This medicine is used to treat:

- **Acromegaly:**

  In people with acromegaly the body makes too much growth hormone, which controls the growth of tissues, organs and bones. This leads to enlargement of the bones, especially of the hands and feet. Other symptoms include headaches, increased sweating, tiredness, numbness of the hands and feet, pain and stiffness in the joints and loss of sexual function. By blocking the excess growth hormone, octreotide can relieve many of these symptoms.

- **Symptoms of certain types of cancer such as carcinoid syndrome and VIPoma:**

  By blocking hormones that are over-produced in these conditions, octreotide can relieve symptoms such as flushing of the skin and severe diarrhoea.

- **People who are having surgery on the pancreas.**

  This medicine helps to lower the chance of complications after the surgery.

Octreotide is a man-made medicine derived from somatostatin (so-MAT-oh-STAT-in), a substance found in the human body. Octreotide is used instead of somatostatin because its effects are stronger and last longer so that it needs to be given only 2 or 3 times a day.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

Your doctor may have prescribed it for another reason.

This medicine is not addictive.

It is available only with a doctor's prescription.

There is very little information on the use of this medicine in children.

Before you use DBL Octreotide Injection

When you must not use it

You must not use Octreotide Injection if you have an allergy to:

- any medicine containing Octreotide
- any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

You must not use this medicine after the expiry date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should use this medicine, talk to your doctor.

Before you start to use it

Tell your doctor if you have allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have, or have had, any of the following medical conditions:

- gallstones
- problems with your blood sugar levels, either too high (diabetes) or too low (hypoglycaemia)
- problems with your liver
- problems with your thyroid
- a history of vitamin B12 deprivation.

Tell your doctor if you are pregnant or plan to become pregnant or are breast-feeding.

Your doctor can discuss with you the risks and benefits involved.

If you have not told your doctor about any of the above, tell him/ her before you use DBL Octreotide Injection.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you get without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and Octreotide may interfere with each other. These include:

- bromocriptine, a medicine used to treat acromegaly
- medicines used to treat diabetes
- cimetidine, a medicine for ulcers
- ciclosporin, a medicine used to suppress the immune system
- quinidine, a medicine used to prevent irregular heartbeats
- terfenadine, a medicine used to treat allergies.

Tell your doctor if you are taking any medicine:

- to control blood pressure (e.g. beta blockers or calcium channel blockers)
- to control fluid or electrolyte balance.

These medicines may be affected by octreotide or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Your doctor and pharmacist have more information on medicines to be careful with or avoid while being treated with this medicine.

How to use DBL Octreotide Injection

Follow all directions given to you by your doctor and pharmacist carefully.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on the label, ask your doctor or pharmacist for help.

How much is given

The dose of DBL Octreotide Injection depends on the condition being treated.

Acromegaly:

treatment is usually started with injections of 0.05 to 0.1 mg every 8 or 12 hours. The dose can then be adjusted depending on how well it blocks growth hormone and relieves symptoms such as tiredness, sweating and headache.

Carcinoid syndrome and VIPoma:

treatment is usually started with injections of 0.05 mg once or twice a day. The dose can be increased if symptoms such as diarrhoea are not relieved.

Surgery on the pancreas:

injections of 0.1 mg are usually given three times a day for one week, starting about an hour before the operation.

How it is given

DBL Octreotide Injection is given as a subcutaneous injection. That means that it is injected into the fat layer just under the skin.

If you are giving the injections yourself

If you will be giving the injections yourself, your doctor or nurse will teach you how to do the injection.

Before using the injection, check the liquid for particles or a change in colour. If you notice anything unusual, do not use the vial.

Once a vial is opened, use it immediately and throw out any liquid that remains.

The vial does not contain any preservative.

Give the injections between meals or at bedtime. Avoid having meals around the time of the injections.

This will help to reduce the chance of stomach upset.

To help prevent irritation or pain at the injection site:

- **choose a new site for each injection. The upper arms, thighs and abdomen are good areas for injection.**
- **make sure the vial is at room temperature before you use it. If it has been in the fridge, take it out half an hour before using it. You can warm it up in your hand but do not try to heat it.**

If you notice pain, stinging, tingling, burning, redness or swelling at the injection site after the injection, gently rub the site for a few seconds.

These side effects rarely last more than 15 minutes after an injection.

If you forget to use it

Inject the dose as soon as you remember, and then go back to using it as you would normally.

It will not do any harm if you miss a dose but some of your symptoms may come back temporarily until you get back on schedule.

Do not use a double dose to make up for the one that you missed.

This may increase the chance of you getting an unwanted side effect.

If you have trouble remembering when to use your medicine, ask your pharmacist for some hints.

If you use too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital if you think that an overdose has happened. Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Some of the symptoms of an overdose may include slow heartbeat,

flushing of the face, cramps in the abdomen, diarrhoea, an empty feeling in the stomach and nausea (feeling sick).

Ask your doctor or pharmacist if you have any concerns.

While you are using DBL Octreotide Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are using DBL Octreotide Injection.

Tell any other doctors, dentists, and pharmacists who treat you that you are using this medicine.

If you are going to have surgery, tell the surgeon or anaesthetist that you are using this medicine.

It may affect other medicines used during surgery.

Women of child-bearing age should use an effective contraceptive method during treatment with DBL Octreotide Injection.

If you become pregnant while you are being treated with this medicine, tell your doctor immediately.

DBL Octreotide Injection should only be used during pregnancy if clearly needed.

Do not breast-feed while using DBL Octreotide Injection.

It is not known whether octreotide passes into breast milk.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not give this medicine to anyone else, even if their symptoms seem to be the same as yours.

Do not use it to treat any other complaints unless your doctor tells you to.

Things to be careful of

Be careful driving or operating machinery until you know how DBL Octreotide Injection affects you.

This medicine may cause dizziness, light-headedness, tiredness, drowsiness in some people. If you have any of these symptoms, do not drive, operate machinery or do anything else that could be dangerous.

Side effects

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well while you are being treated with DBL Octreotide Injection.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the following lists of side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor, nurse or pharmacist if you notice any of the following and they worry you:

- irritation, pain, redness, rash or swelling at the injection site
- loss of appetite
- indigestion, nausea or vomiting
- cramps
- feeling of bloating or wind
- constipation, diarrhoea or other change in bowel motions
- stomach pain or tenderness
- discoloured stools
- fatty stools
- headache
- dizziness or light headedness
- swelling of hands or feet due to excess fluid
- tiredness or weakness
- flushing of the skin
- temporary hair loss
- changes in the rhythm of your heart beat
- shortness of breath.

The above list includes the more common side effects of your medicine.

If any of the following happen, tell your doctor or nurse immediately or go to Accident and Emergency at your nearest hospital:

- symptoms of an allergic reaction including shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- severe pain, tenderness or swelling in the stomach or abdomen, which may be accompanied by fever, nausea and vomiting, yellowing of the skin and eyes, loss of appetite, feeling unwell, itching, light coloured urine (symptoms of a possible problem with your liver, pancreas or gall bladder)
- symptoms of low blood glucose (hypoglycaemia), including sweating, trembling, dizziness, weakness, hunger, palpitations (feeling of fast or irregular heartbeat) and fatigue
- symptoms of high blood glucose (hyperglycaemia), including lethargy or tiredness, headache, thirst, passing large amounts of urine, and blurred vision
- symptoms of an underactive thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight, tiredness,

feeling cold, or swelling at the front of the neck

- unusually slow heartbeat
- increased bleeding or bruising (could be low levels of platelets in the blood).

The above list includes very serious side effects. You may need urgent medical attention

Tell your doctor, nurse or pharmacist if you notice anything that is making you feel unwell.

Other side effects not listed above may also occur in some people.

After using DBL Octreotide Injection

Storage

Keep your medicine in the original pack until it is time to use it.

If you take your medicine out of the pack it may not keep well.

Store your medicine in the refrigerator. Do not freeze them.

Do not store DBL Octreotide Injection or any other medicine in the bathroom or near a sink. Do not leave it on a window sill or in the car.

Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop using this medicine or you find that the expiry date has passed or the vials have been left out of the fridge for too long, ask your pharmacist what to do with any medicine you have left over.

Product description

What it looks like

DBL Octreotide Injection comes in 1 mL glass vials containing a clear colourless liquid free of foreign matter. It is available in packs of 5.

Ingredients

DBL Octreotide Injection contains 0.05 mg, 0.1 mg or 0.5 mg of octreotide (as octreotide acetate) as the active ingredient. It also contains:

- glacial acetic acid
- sodium acetate trihydrate
- sodium chloride
- water for injections.

This medicine does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

Sponsor

DBL™ Octreotide Injection is supplied by:

Pfizer Australia Pty Ltd

Sydney NSW

Toll Free Number: 1800 675 229

www.pfizer.com.au

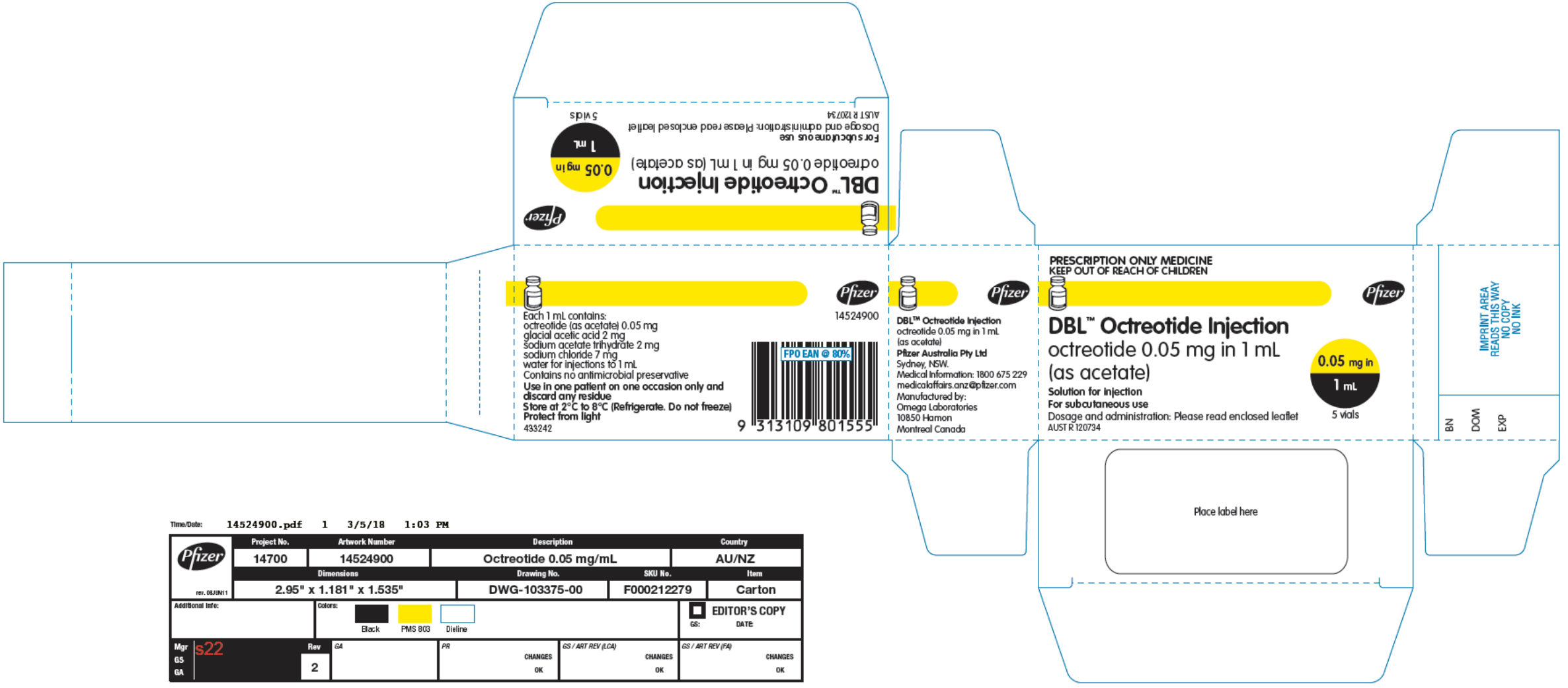
This leaflet was updated in March 2021.

Australian Registration Numbers:

0.05 mg/ 1 mL AUST R 120734

0.1 mg/ 1 mL AUST R 120735

0.5 mg/1 mL AUST R 120736



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rev. 08JUN11

Additional Info:

Colors: Black, PMS 803, Dieline

☐ EDITOR'S COPY
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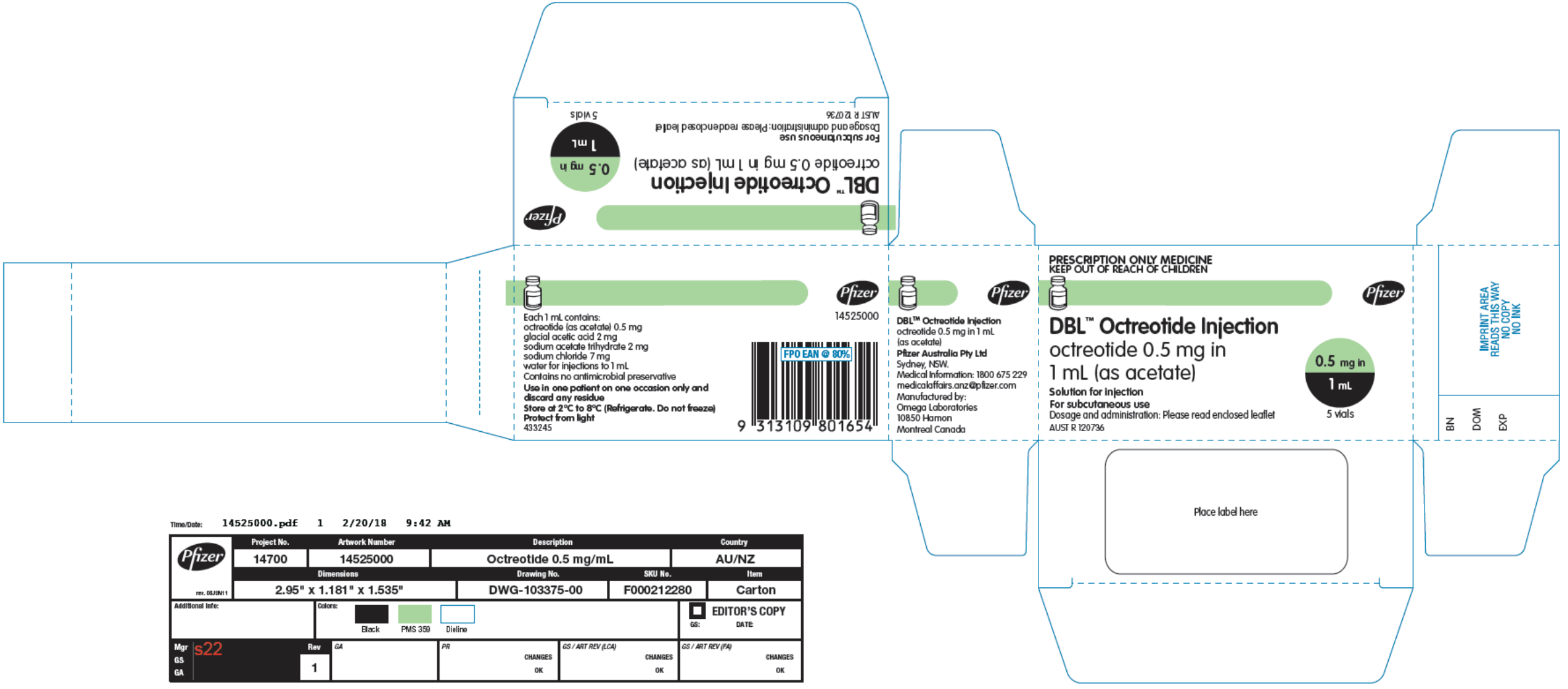

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rev. 08JUN11

Additional Info:

Colors: Black, PMS 359, Dieline

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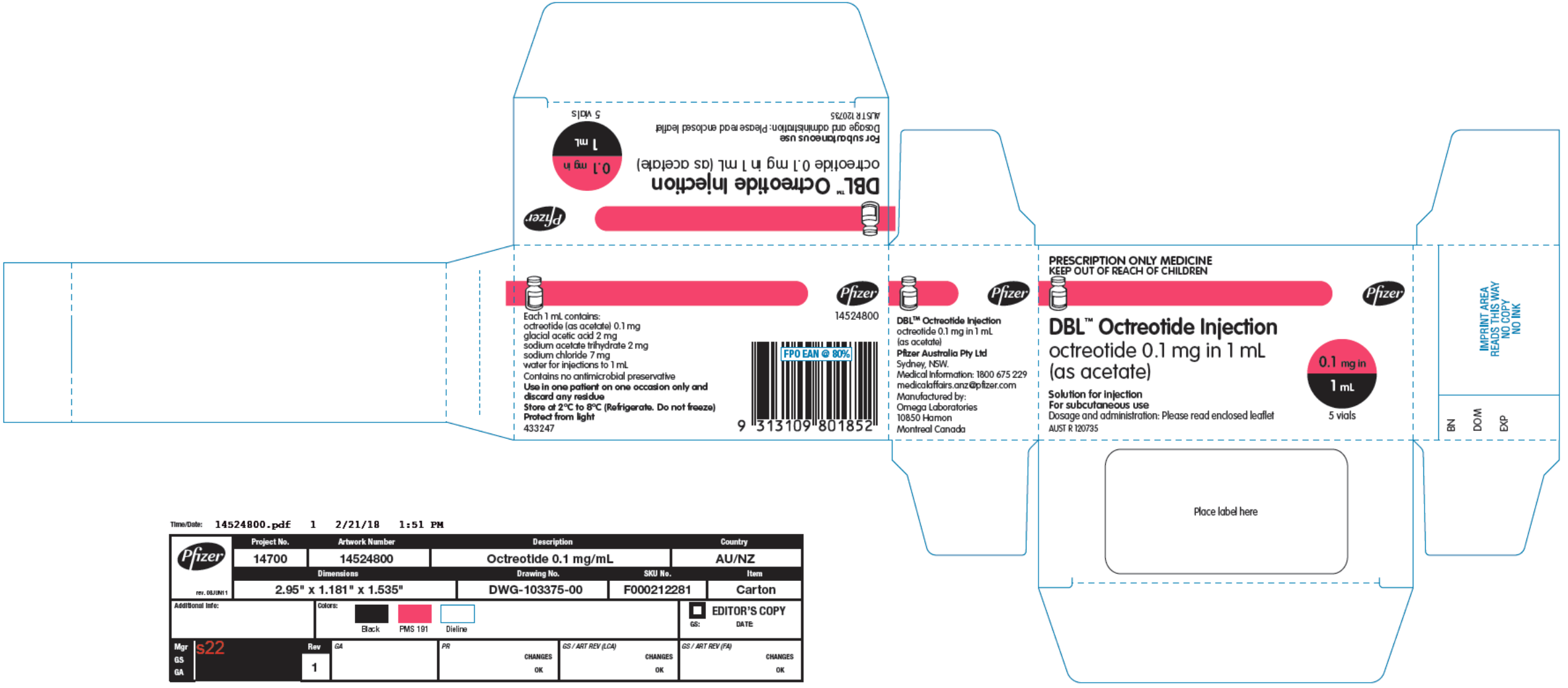

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rev. 08JUN11

Additional Info:

Colors: Black, PMS 191, Dieline

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GS: DATE

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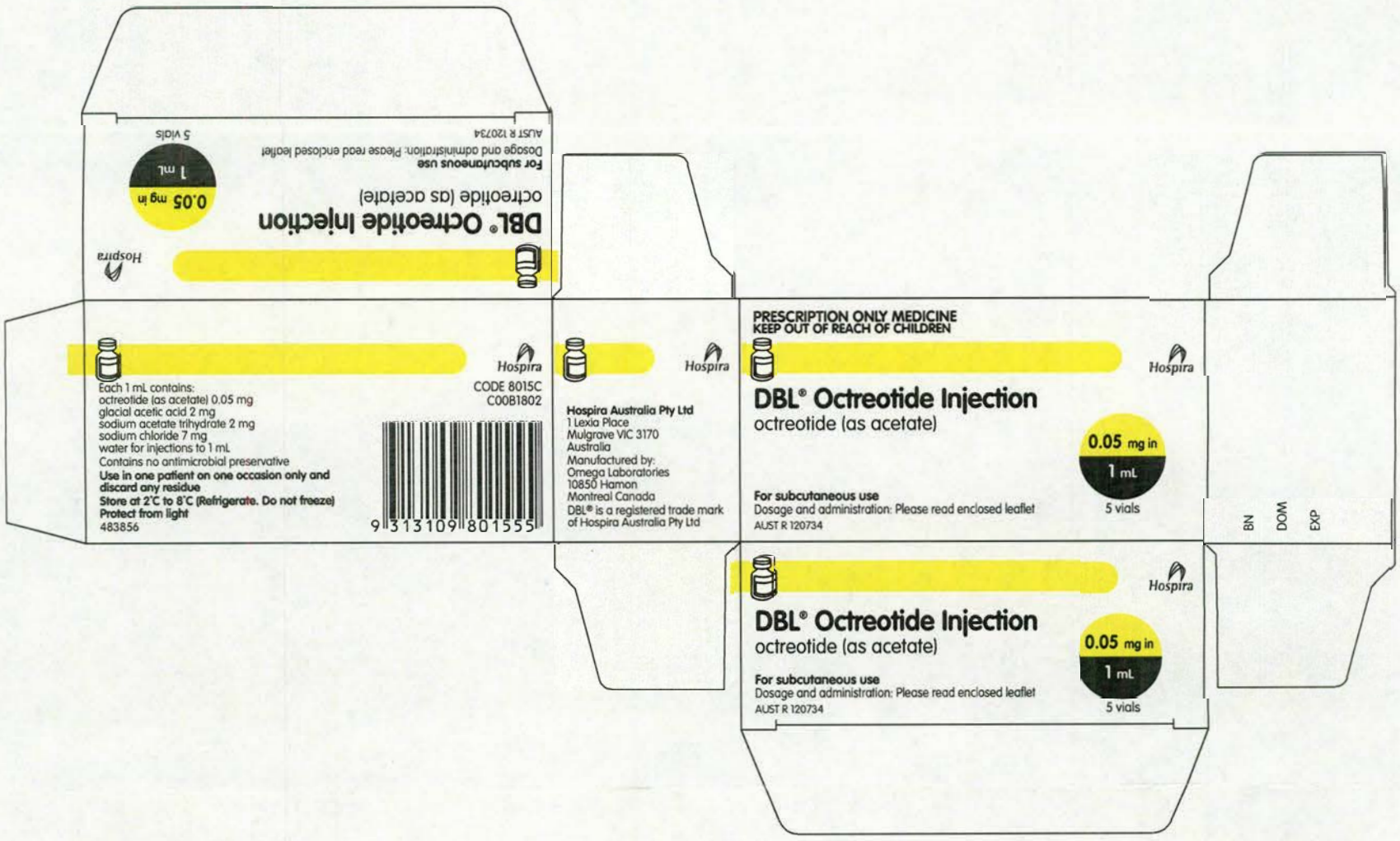

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	Artworker/Designer	jk

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			Omega
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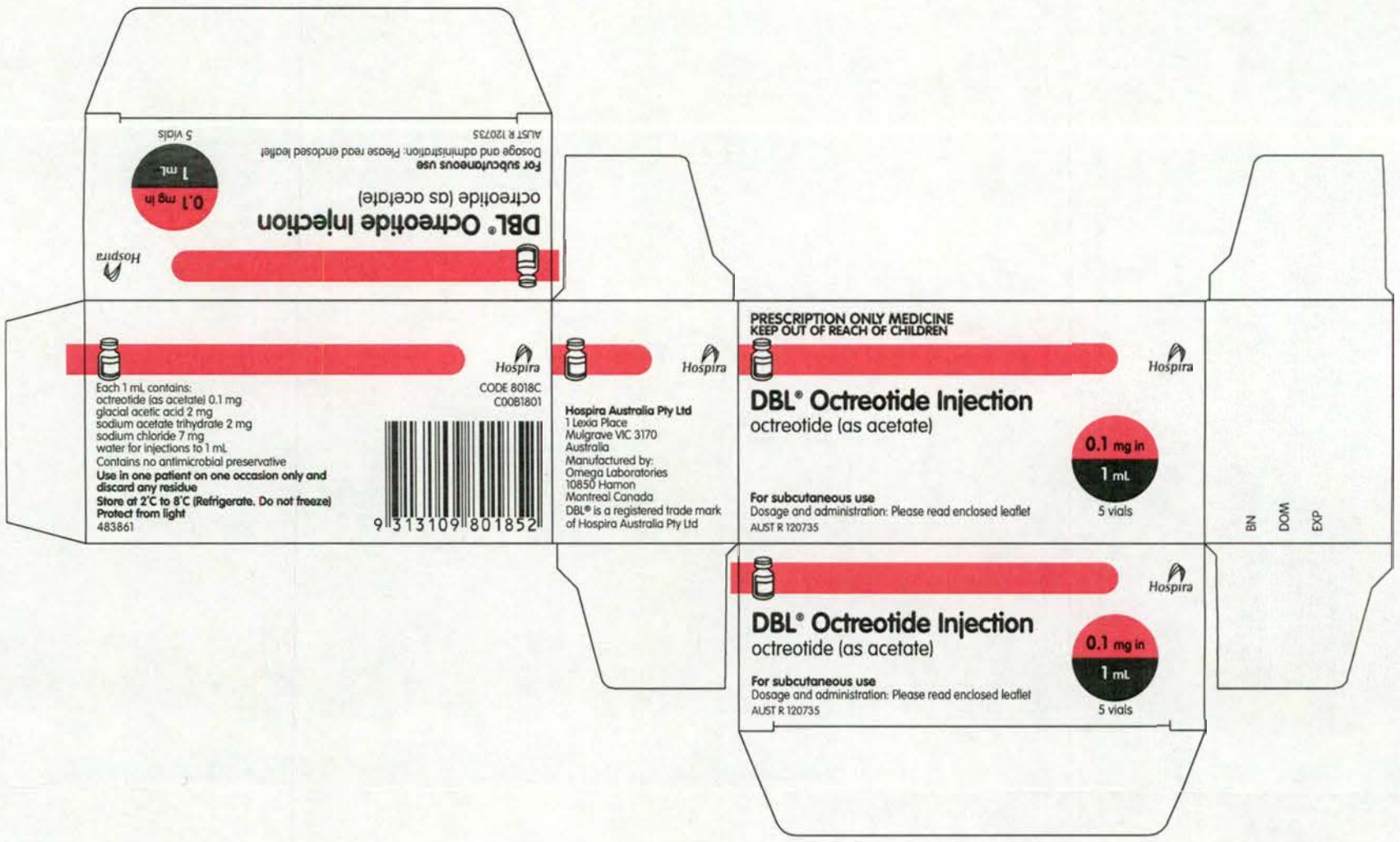

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	Artworker/Designer	jk

Hospira Australia Pty Ltd			in-licenced
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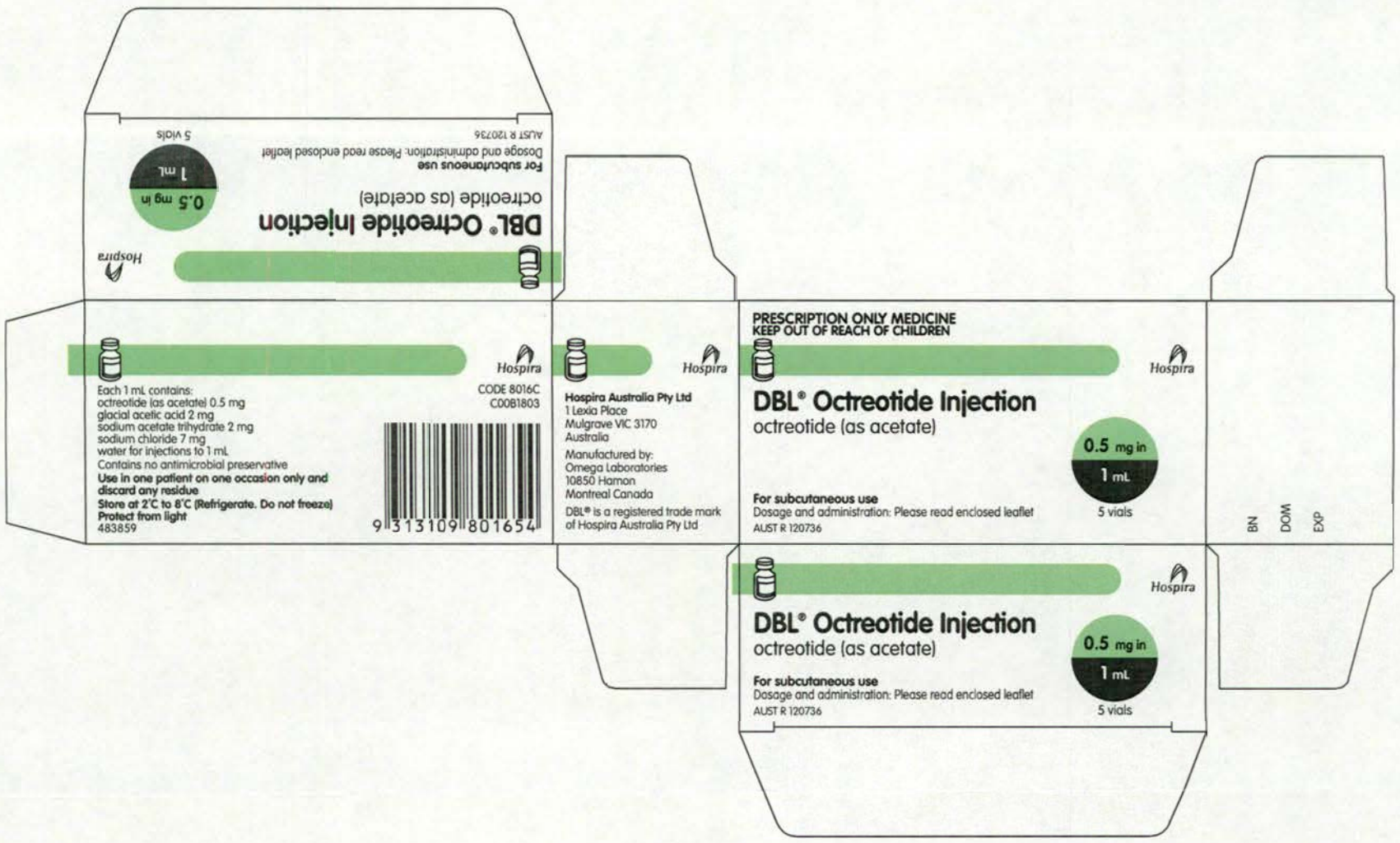

Hospira Australia Pty Ltd			in-licenced
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		Label 17.46 x 44.45 mm	

Colour/s		
Black C 359 C Light Green	Artwork Version	5
	Date of Preparation	28/04/08
	Artworker/Designer	jk

DBL™ OCTREOTIDE INJECTION

NAME OF THE MEDICINE
Octreotide

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

CAS number: 79517-01-4. (octreotide acetate)
MW: 1019.3 (free peptide)

DESCRIPTION
DBL™ Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

Each 1 mL vial contains 0.05 mg, 0.1 mg or 0.5 mg octreotide (as acetate) with the excipients, glacial acetic acid, sodium acetate trihydrate, sodium chloride, water for injections.

PHARMACOLOGY
Pharmacodynamics
Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

In healthy subjects octreotide, like somatostatin, has been shown to inhibit:
- Release of growth hormone (GH) stimulated by arginine, exercise and insulin-induced hypoglycaemia
- Postprandial release of insulin, glucagon, gastrin, other peptides of the GEP system, and arginine-stimulated release of insulin and glucagon
- Thyrotropin releasing hormone (TRH) stimulated release of thyroid stimulating hormone (TSH).

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

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

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

related to their tumours despite previous therapies which include surgery, hepatic artery embolisation and various chemotherapies, e.g. streptozotocin and 5-fluorouracil.

Effects of octreotide in the different tumour types are as follows:

- *Carcinoid tumours:* Administration of octreotide may result in improvement of symptoms, particularly of flush episodes and severe diarrhoea. In some cases this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid. In the event of no beneficial response to octreotide treatment, continuation of therapy beyond one week at the maximum tolerated dose is not recommended, although in non-responders no serious sustained adverse drug effects have been reported.
- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Pharmacokinetics

Absorption:

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

Distribution:

The distribution of octreotide from plasma was rapid ($t\frac{1}{2}_{\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

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

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

The elimination capacity may be reduced in patients with liver cirrhosis (see **PRECAUTIONS: Use in patients with impaired hepatic function**), but not in patients with fatty liver disease.

INDICATIONS

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

  Octreotide is not an antitumour therapy and is not curative in these patients.
- For reduction of the incidence of complications following pancreatic surgery.

CONTRAINDICATIONS
Hypersensitivity to octreotide or to any component of the formulation.

PRECAUTIONS
Development of gallstones
Development of gallstones has been reported in 15 to 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 to 20%. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

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

Gastro-entero-pancreatic endocrine tumours
In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

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

Patients with type I diabetes mellitus requiring insulin therapy may have their insulin requirements reduced by administration of octreotide. In non-diabetic patients and patients with type II diabetes mellitus who have partially intact insulin reserves, octreotide administration can result in prandial increases in glycaemia (see **ADVERSE EFFECTS**).

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

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 is necessary.

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

Use in the Elderly
In elderly patients treated with octreotide, there was no evidence for reduced tolerability or altered dosage requirements.

Use in Children
Experience with octreotide in children is very limited.

Carcinogenesis, mutagenesis and impairment of fertility
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. 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.

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

suppression of growth hormone. No adequate and well controlled studies have been performed in pregnant women. Therefore, this drug should be used in pregnancy only if clearly needed.

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.

Use in Lactation
Experience with octreotide in nursing women is not available. In such patients the drug should be used only under compelling circumstances.

INTERACTIONS WITH OTHER MEDICINES

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

Octreotide has been reported to produce a reduction in the intestinal absorption of cyclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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, such as insulin, affecting glucose metabolism may be required following initiation of octreotide therapy in patients with diabetes (see **PRECAUTIONS: Effects on glucose regulation**).

ADVERSE EFFECTS

The main side effects encountered with octreotide administration are local injection site reactions and gastrointestinal effects.

Local reactions
Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness and swelling. They rarely last more than fifteen 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.

Gastrointestinal system
Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea, and steatorrhoea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder
Prolonged use of octreotide may result in gallstone formation (see **PRECAUTIONS**).

Pancreas
Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation (see **PRECAUTIONS**) and impair postprandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been observed.

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

Liver
There have been isolated reports of hepatic or biliary dysfunctions associated with octreotide administration. These consist of the following:

- acute hepatitis without cholestasis where normalisation of transaminase values on withdrawal of octreotide has occurred.
- the slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Body as a whole
Rarely, transient hair loss has been reported. Rare cases of hypersensitivity skin reactions and very rare cases of anaphylactic reactions have been reported. Bradycardia has been reported very rarely.

Other
Other reactions that occur less frequently include headache, dizziness/light-headedness, fatigue, asthenia/weakness, flushing, oedema.

One case of clinical hypothyroidism has been reported in a patient who had received 1500 mcg octreotide daily for 19 months.

DOSAGE AND ADMINISTRATION

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 on clinical symptoms and on tolerability. In most patients the optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with 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, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 mcg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

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

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. 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 Injection contains no antimicrobial agent. Product is for single use in one patient only. Discard any remaining contents.

Use in the Elderly

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

Use in Children

Experience with octreotide in children is very limited.

OVERDOSAGE

Symptoms

No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental

overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

Treatment
The management of overdosage is symptomatic.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26. In New Zealand, call 0800 764 766).

PRESENTATION AND STORAGE CONDITIONS

DBL™ Octreotide Injection is available as:

0.05 mg/1 mL vial, 5 pack	AUST R 120734
0.1 mg/1 mL vial, 5 pack	AUST R 120735
0.5 mg/1 mL vial, 5 pack	AUST R 120736

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

NAME AND ADDRESS OF SPONSOR

Australian Sponsor:
Hospira Australia Pty Ltd
ABN 58 097 064 330
Level 3
500 Collins Street
Melbourne Vic 3000
Australia

New Zealand Sponsor:
Hospira NZ Limited
23 Haining Street
Te Aro
Wellington
New Zealand

POISON SCHEDULE OF THE MEDICINE

All States and A.C.T.—S.4.

Date of TGA approval: 20 June 2008

Date of most recent amendment: 30 January 2012

Hospira Australia Pty Ltd			**in-licenced**
			Omega
		Carton 75 x 30 x 39 mm	

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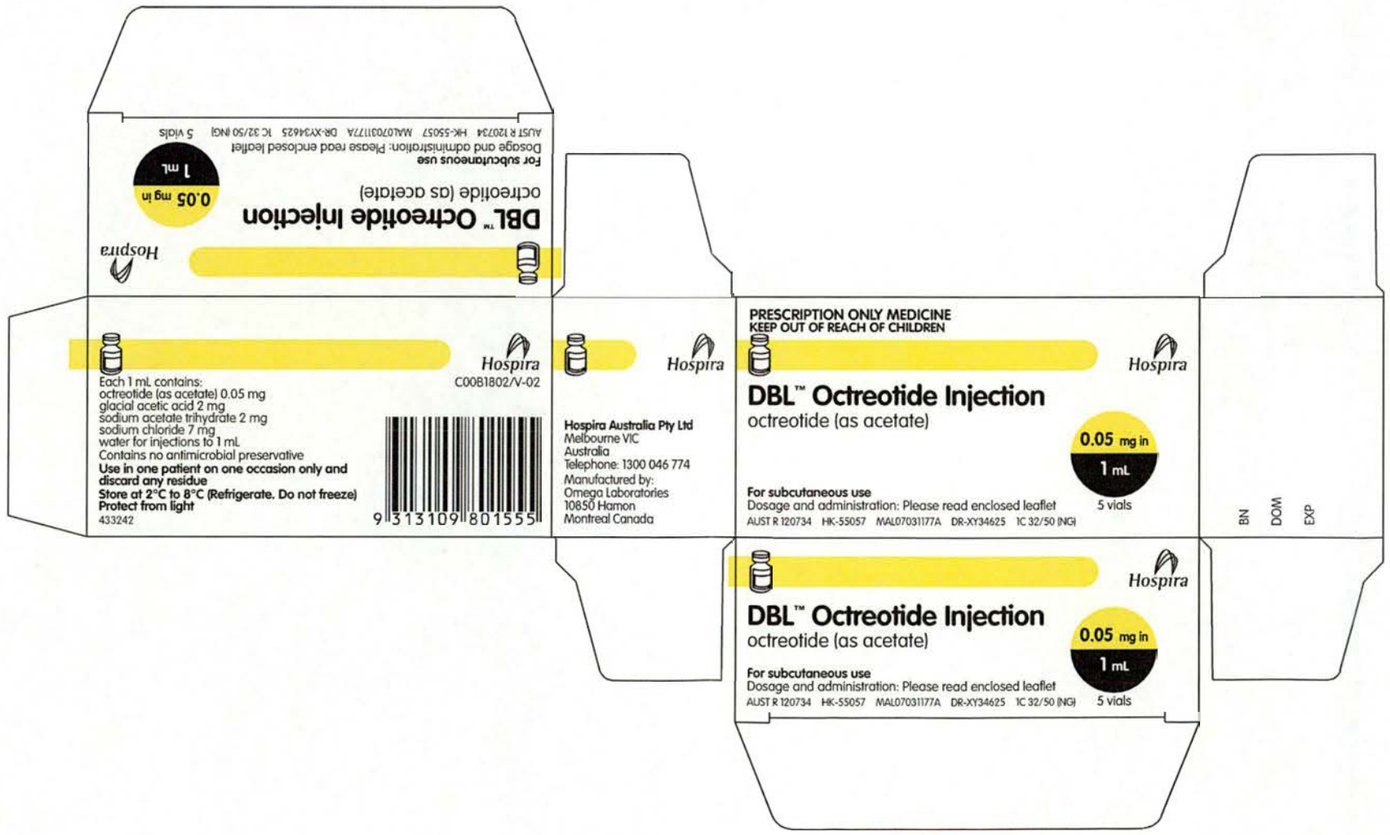
	Date of Preparation	18/01/12
	Artworker/Designer	jn



Hospira Australia Pty Ltd			**in-licenced**
			Omega
		Carton 75 x 30 x 39 mm	

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	Date of Preparation	20/01/12
	Artworker/Designer	jn

Hospira Australia Pty Ltd			**in-licenced**
			Omega
		Carton 75 x 30 x 39 mm	

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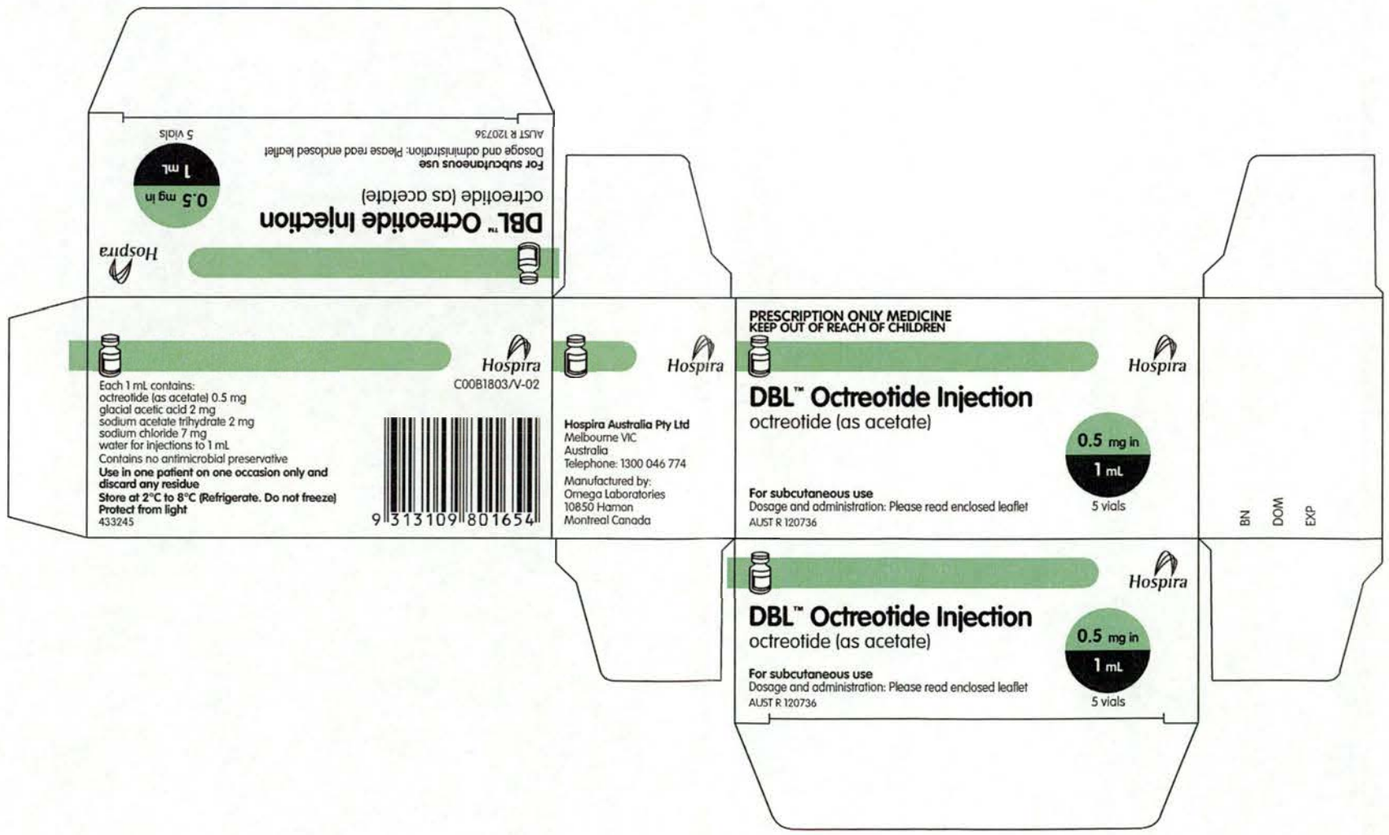
	Date of Preparation	20/01/12
	Artworker/Designer	jn



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OCTREOTIDE INJECTION

NAME OF THE DRUG
Octreotide

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

CAS number: 79517-01-4. (octreotide acetate)
MW: 1019.3 (free peptide)

DESCRIPTION
Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

Each 1 mL vial contains 0.05 mg, 0.1 mg or 0.5 mg octreotide (as acetate) with the excipients, glacial acetic acid, sodium acetate trihydrate, sodium chloride, water for injections

PHARMACOLOGY
Pharmacodynamics
Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

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

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

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

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

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

related to their tumours despite previous therapies which include surgery, hepatic artery embolisation and various chemotherapies, e.g. streptozotocin and 5-fluorouracil.

Effects of octreotide in the different tumour types are as follows:

- *Carcinoid tumours:* Administration of octreotide may result in improvement of symptoms, particularly of flush episodes and severe diarrhoea. In some cases this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid. In the event of no beneficial response to octreotide treatment, continuation of therapy beyond one week at the maximum tolerated dose is not recommended, although in non-responders no serious sustained adverse drug effects have been reported.
- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Pharmacokinetics

Absorption:

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

Distribution:

The distribution of octreotide from plasma was rapid ($t\frac{1}{2}_{\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

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Elimination:

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

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

The elimination capacity may be reduced in patients with liver cirrhosis (see **PRECAUTIONS: Use in patients with impaired hepatic function**), but not in patients with fatty liver disease.

INDICATIONS

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

  Octreotide is not an antitumour therapy and is not curative in these patients.
- For reduction of the incidence of complications following pancreatic surgery.

CONTRAINDICATIONS

Hypersensitivity to octreotide or to any component of the formulation.

PRECAUTIONS

Development of gallstones
Development of gallstones has been reported in 15 to 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 to 20%. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

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

Gastro-entero-pancreatic endocrine tumours
In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

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

Patients with type I diabetes mellitus requiring insulin therapy may have their insulin requirements reduced by administration of octreotide. In non-diabetic patients and patients with type II diabetes mellitus who have partially intact insulin reserves, octreotide administration can result in prandial increases in glycaemia (see **ADVERSE REACTIONS**).

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

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 is necessary.

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

Use in the Elderly
In elderly patients treated with octreotide, there was no evidence for reduced tolerability or altered dosage requirements.

Use in Children
Experience with octreotide in children is very limited.

Carcinogenesis, mutagenesis and impairment of fertility
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. 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.

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

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performed in pregnant women. Therefore, this drug should be used in pregnancy only if clearly needed.

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 maybe reversible.

Use in Lactation
Experience with octreotide in nursing women is not available. In such patients the drug should be used only under compelling circumstances.

INTERACTIONS WITH OTHER DRUGS

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

Octreotide has been reported to produce a reduction in the intestinal absorption of cyclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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 Injection. Adjustment of the dosage of drugs, such as insulin, affecting glucose metabolism may be required following initiation of Octreotide Injection therapy in patients with diabetes (see **PRECAUTIONS: Effects on glucose regulation**).

ADVERSE REACTIONS

The main side effects encountered with octreotide administration are local injection site reactions and gastrointestinal effects.

Local reactions
Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness and swelling. They rarely last more than fifteen minutes. Local

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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.

Gastrointestinal system
Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea, and steatorrhoea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder
Prolonged use of octreotide may result in gallstone formation (see **PRECAUTIONS**).

Pancreas
Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation (see **PRECAUTIONS**) and impair postprandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been observed.

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

Liver
There have been isolated reports of hepatic or biliary dysfunctions associated with octreotide administration. These consist of the following:

- acute hepatitis without cholestasis where normalisation of transaminase values on withdrawal of octreotide has occurred.
- the slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Body as a whole
Rarely, transient hair loss has been reported. Rare cases of hypersensitivity skin reactions and very rare cases of anaphylactic reactions have been reported. Bradycardia has been reported very rarely.

Other
Other reactions that occur less frequently include headache, dizziness/light-headedness, fatigue, asthenia/weakness, flushing, oedema.

One case of clinical hypothyroidism has been reported in a patient who had received 1500 mcg octreotide daily for 19 months.

DOSAGE AND ADMINISTRATION

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 on clinical symptoms and on tolerability. In most patients the optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not

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

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

Gastro-entero-pancreatic endocrine tumours
Initially 0.05 mg once or twice daily by subcutaneous injection. De pending on clinical response, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 mcg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

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

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. 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.
Octreotide Injection contains no antimicrobial agent. Product is for single use in one patient only. Discard any remaining contents.

Use in the Elderly
In elderly patients treated with octreotide, there was no evidence for reduced tolerability or altered dosage requirements.

Use in Children
Experience with octreotide in children is very limited.

OVERDOSAGE

Symptoms
No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

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Treatment
The management of overdosage is symptomatic.

PRESENTATION

Octreotide Injection is available as:

0.05 mg/1 mL vial, 5 pack	AUST R XXXXX
0.1 mg/1 mL vial, 5 pack	AUST R XXXXX
0.5 mg/1 mL vial, 5 pack	AUST R XXXXX.

STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

NAME AND ADDRESS OF SPONSOR

Mayne Pharma Pty Ltd
ABN 58 097 067 330
Level 21
390 St Kilda Road
Melbourne Vic 2004
Australia

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All States and A.C.T.—S.4.

Date of TGA approval: xx xx xxxx

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Octreotide Injection

Octreotide *(ok-tree-oh-tide)*

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Octreotide Injection. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you being given Octreotide Injection against the benefits they expect it will have for you.

If you have any concerns about being given this medicine, ask your doctor or pharmacist.

Keep this leaflet.
You may need to read it again.

What Octreotide Injection is used for

This medicine is used to treat:

- Acromegaly

In people with acromegaly the body makes too much growth hormone, which controls the growth of tissues, organs and bones. This leads to enlargement of the bones, especially of the hands and feet. Other symptoms include headaches, increased sweating, tiredness, numbness of the hands and feet, pain and stiffness in the joints and loss of sexual function. By blocking the excess growth hormone, octreotide can relieve many of these symptoms.

- Symptoms of certain types of cancer such as carcinoid syndrome and VIPoma.

By blocking hormones that are over-produced in these conditions, octreotide can relieve symptoms such as flushing of the skin and severe diarrhoea.

- People who are having surgery on the pancreas. This medicine helps to lower the chance of complications after the surgery.

Octreotide is a man-made medicine derived from somatostatin, a substance found in the human body. Octreotide is used instead of somatostatin because its effects are stronger and last longer so that it needs to be given only 2 or 3 times a day.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.
Your doctor may have prescribed it for another reason.

This medicine is not addictive.

It is available only with a doctor's prescription.

There is very little information on the use of this medicine in children.

Before you are given Octreotide Injection

When you must not be given it

You must not be given Octreotide Injection if you have an allergy to:

- any medicine containing octreotide
- any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

You must not use this medicine after the expiry date printed on the pack or if the packaging is torn or shows signs of tampering.
If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should be given this medicine, talk to your doctor.

Before you are given it

Tell your doctor if you have allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have, or have had, any of the following medical conditions:

- gallstones
- problems with your blood sugar levels, either too high (diabetes) or too low (hypoglycaemia)
- problems with your liver.

Tell your doctor if you are pregnant or plan to become pregnant or are breast-feeding.
Your doctor can discuss with you the risks and benefits involved.

If you have not told your doctor about any of the above, tell him/her before you are given Octreotide Injection.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you get without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and octreotide may interfere with each other. These include:

- bromocriptine, a medicine used to treat acromegaly
- medicines used to treat diabetes

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- cimetidine, a medicine for ulcers
- cyclosporine, a medicine used to suppress the immune system
- quinidine, a medicine used to prevent irregular heartbeats.

These medicines may be affected by octreotide or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Your doctor and pharmacist have more information on medicines to be careful with or avoid while being treated with this medicine.

How Octreotide Injection is given

Follow all directions given to you by your doctor and pharmacist carefully.
They may differ from the information contained in this leaflet.

If you do not understand the instructions on the label, ask your doctor or pharmacist for help.

How much is given

The dose of Octreotide Injection depends on the condition being treated.

Acromegaly: treatment is usually started with injections of 0.05 to 0.1 mg every 8 or 12 hours. The dose can then be adjusted depending on how well it blocks growth hormone and relieves symptoms such as tiredness, sweating and headache.

Carcinoid syndrome and VIPoma: treatment is usually started with injections of 0.05 mg once or twice a day. The dose can be increased if symptoms such as diarrhoea are not relieved.

Surgery on the pancreas: injections of 0.1 mg are usually given three times a day for one week, starting about an hour before the operation.

How it is given

Octreotide Injection is given as a subcutaneous injection. That means that it is injected into the fat layer just under the skin.

If you are giving the injections yourself

If you will be giving the injections yourself, your doctor or nurse will teach you how to do the injection.

Before using an Octreotide Injection ampoule, check the liquid for particles or a change in colour. If you notice anything unusual, do not use the ampoule.

Once an ampoule is opened, use it immediately and throw out any liquid that remains.
The ampoule does not contain any preservative.

Give the injections between meals or at bedtime. Avoid having meals around the time of the injections.
This will help to reduce the chance of stomach upset.

To help prevent irritation or pain at the injection site:

- **choose a new site for each injection.** The upper arms, thighs and abdomen are good areas for injection.
- **make sure the ampoule is at room temperature before you use it.** If it has been in the fridge, take it out half an hour before using it. You can warm it up in your hand but don't try to heat it.

If you notice pain, stinging, tingling, burning, redness or swelling at the injection site after the injection, gently rub the site for a few seconds.
These side effects rarely last more than 15 minutes after an injection.

If you forget to use it

Inject the dose as soon as you remember, and then go back to using it as you would normally.
It won't do any harm if you miss a dose but some of your symptoms may come back temporarily until you get back on schedule.

Do not use a double dose to make up for the one that you missed.
This may increase the chance of you getting an unwanted side effect.

If you have trouble remembering when to use your medicine, ask your pharmacist for some hints.

If you use too much (Overdose)

Immediately telephone your doctor or Poisons Information Centre (telephone 13 11 26), or go to Accident and Emergency at your nearest hospital if you think that an overdose has happened. Do this even if there are no signs of discomfort or poisoning.
You may need urgent medical attention.

Some of the symptoms of an overdose may include slow heartbeat, flushing of the face, cramps in the abdomen, diarrhoea, an empty feeling in the stomach and nausea (feeling sick).

Ask your doctor or pharmacist if you have any concerns.

While you are being given Octreotide Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being given Octreotide Injection.

Tell any other doctors, dentists, and pharmacists who treat you that you are being given this medicine.

If you are going to have surgery, tell the surgeon or anaesthetist that you are being given this medicine.
It may affect other medicines used during surgery.

If you become pregnant while you are being treated with this medicine, tell your doctor immediately.

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Keep all of your doctor's appointments so that your progress can be checked.
Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not give this medicine to anyone else, even if their symptoms seem to be the same as yours.

Do not use it to treat any other complaints unless your doctor tells you to.

Things to be careful of

Be careful driving or operating machinery until you know how Octreotide Injection affects you.
This medicine may cause dizziness, light-headedness, tiredness, drowsiness in some people. If you have any of these symptoms, do not drive, operate machinery or do anything else that could be dangerous.

Side effects

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well while you are being treated with Octreotide Injection.
All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the following lists of side effects.
You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor, nurse or pharmacist if you notice any of the following and they worry you:
- irritation or pain at the injection site
- loss of appetite
- nausea or vomiting
- cramps
- feeling of bloating or wind
- diarrhoea or other change in bowel motions
- headache
- dizziness or light headedness
- swelling of hands or feet due to excess fluid
- tiredness or weakness
- flushing of the skin
- temporary hair loss.

The above list includes the more common side effects of your medicine.

If any of the following happen, tell your doctor or nurse immediately or go to Accident and Emergency at your nearest hospital:
- symptoms of an allergic reaction including shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.
- severe pain, tenderness or swelling in the stomach or abdomen, which may be accompanied by fever, nausea and vomiting (symptoms of a possible problem with your liver, pancreas or gall bladder)
- symptoms of low blood glucose (hypoglycaemia), including sweating, trembling, dizziness, weakness, hunger, palpitations (feeling of fast or irregular heartbeat) and fatigue
- symptoms of high blood glucose (hyperglycaemia), including lethargy or tiredness, headache, thirst, passing large amounts of urine, and blurred vision
- unusually slow heartbeat.

The above list includes very serious side effects. You may need urgent medical attention

Tell your doctor, nurse or pharmacist if you notice anything that is making you feel unwell.
Other side effects not listed above may also occur in some people.

After using Octreotide Injection

Storage

Keep your medicine in the original pack until it is time to use it.
If you take your medicine out of the pack it may not keep well.

Your medicine can be stored for up to 2 weeks in a cool dry place where the temperature stays below 25°C, and is protected from light.

If you are storing your medicine for longer than 2 weeks, keep them in the refrigerator. Do not freeze them.

Do not store Octreotide Injection or any other medicine in the bathroom or near a sink. Do not leave it on a window sill or in the car.
Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.
A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If any of your medicine has been left out of the fridge for longer than 2 weeks, do not use them.

If your doctor tells you to stop using this medicine or you find that the expiry date has passed or the ampoules have been left out of the fridge for too long, ask your pharmacist what to do with any medicine you have left over.

Product description

What it looks like

Octreotide Injection comes in 1 mL glass vials containing a clear colourless liquid. It is available in packs of 5.

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Ingredients

Octreotide Injection contains 0.05 mg, 0.1 mg or 0.5 mg of octreotide (as octreotide acetate) as the active ingredient. It also contains:

- glacial acetic acid
- sodium acetate trihydrate
- sodium chloride
- water for injections

This medicine does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

Supplier

Mayne Pharma Pty Ltd
ABN 58 097 064 330
1 Lexia Place
Mulgrave VIC 3170
Australia

This leaflet was prepared in September 2005

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AUST R number(s):

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			Omega
		Carton 75 x 30 x 39 mm	

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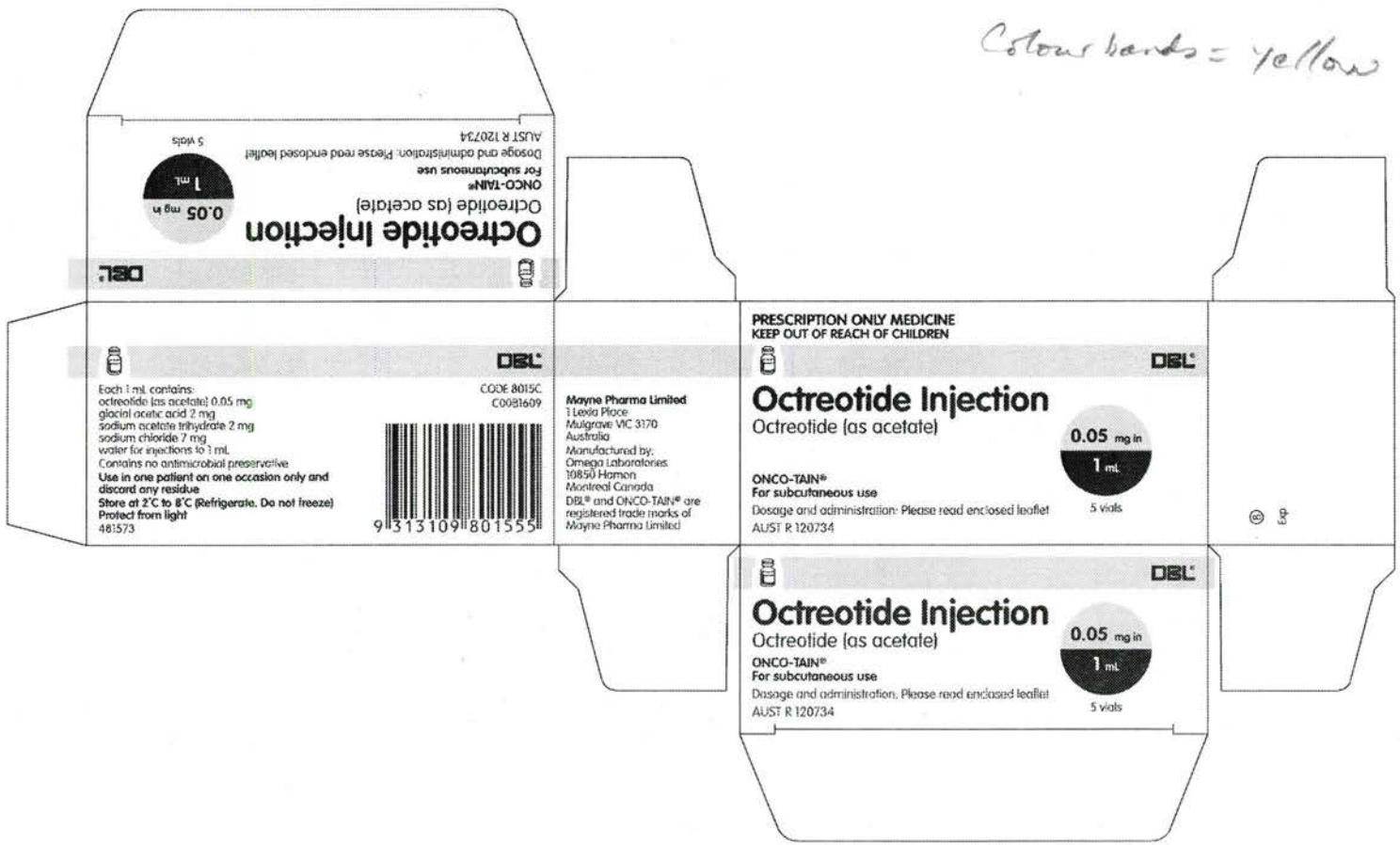

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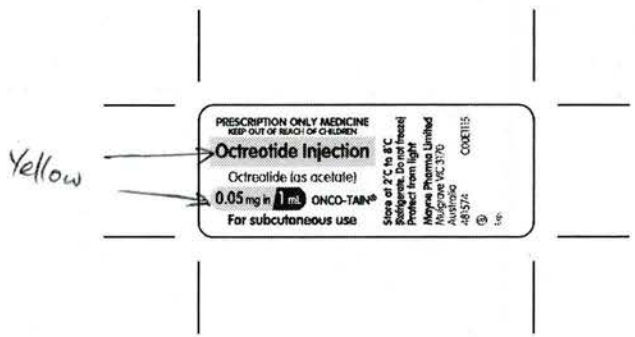

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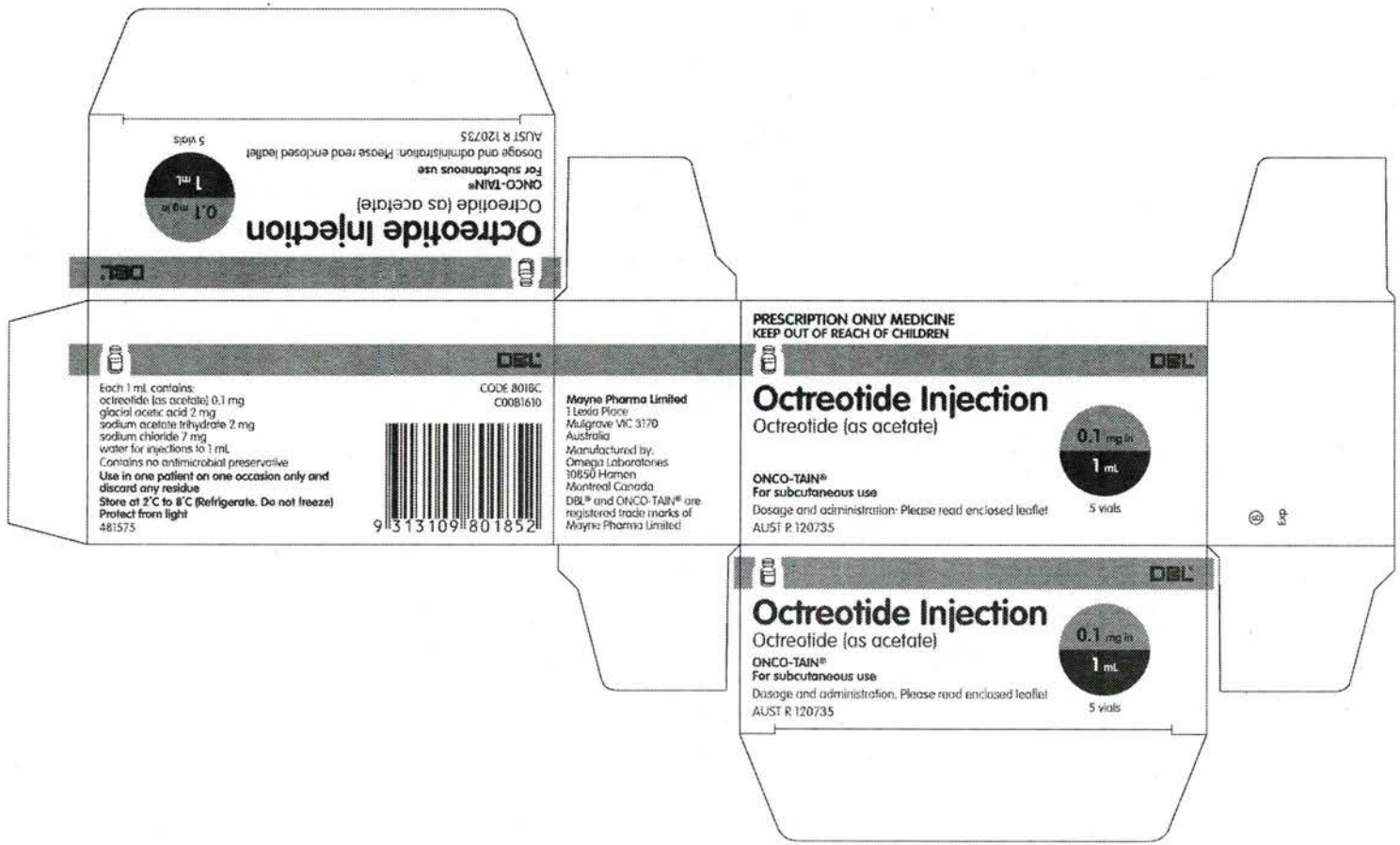

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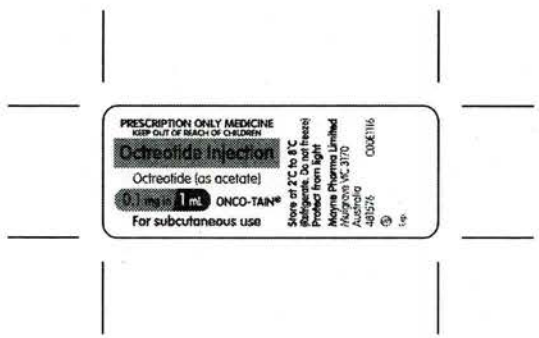

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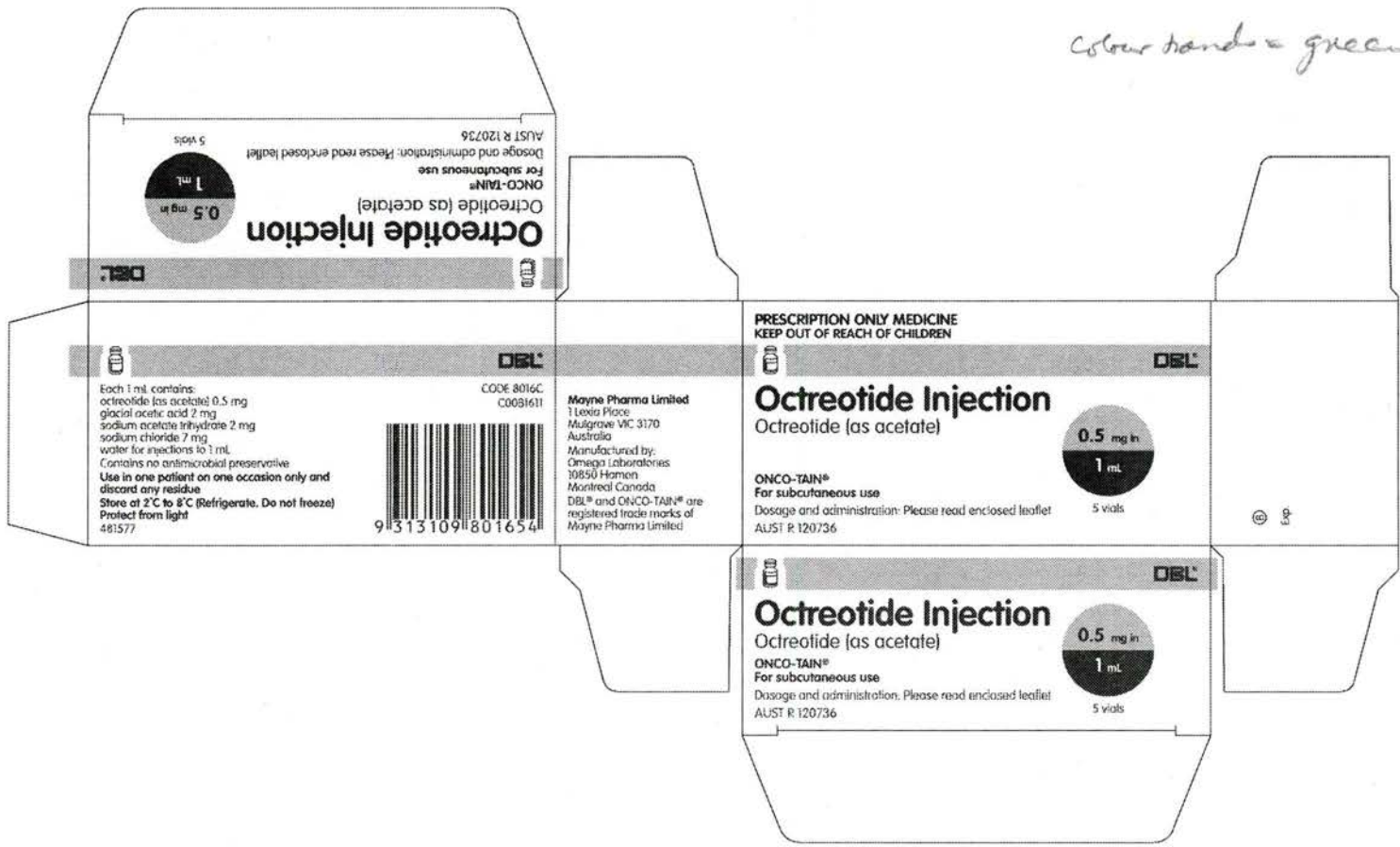

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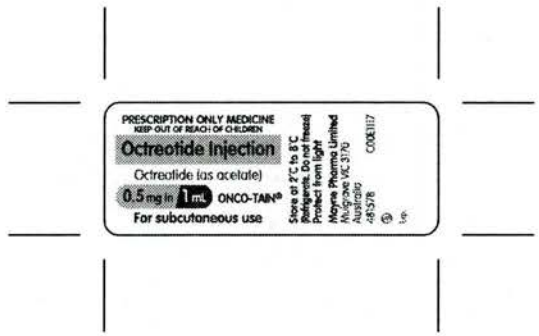

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	Artworker/Designer	jn

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Colour/s

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- 191 C Dark Pink

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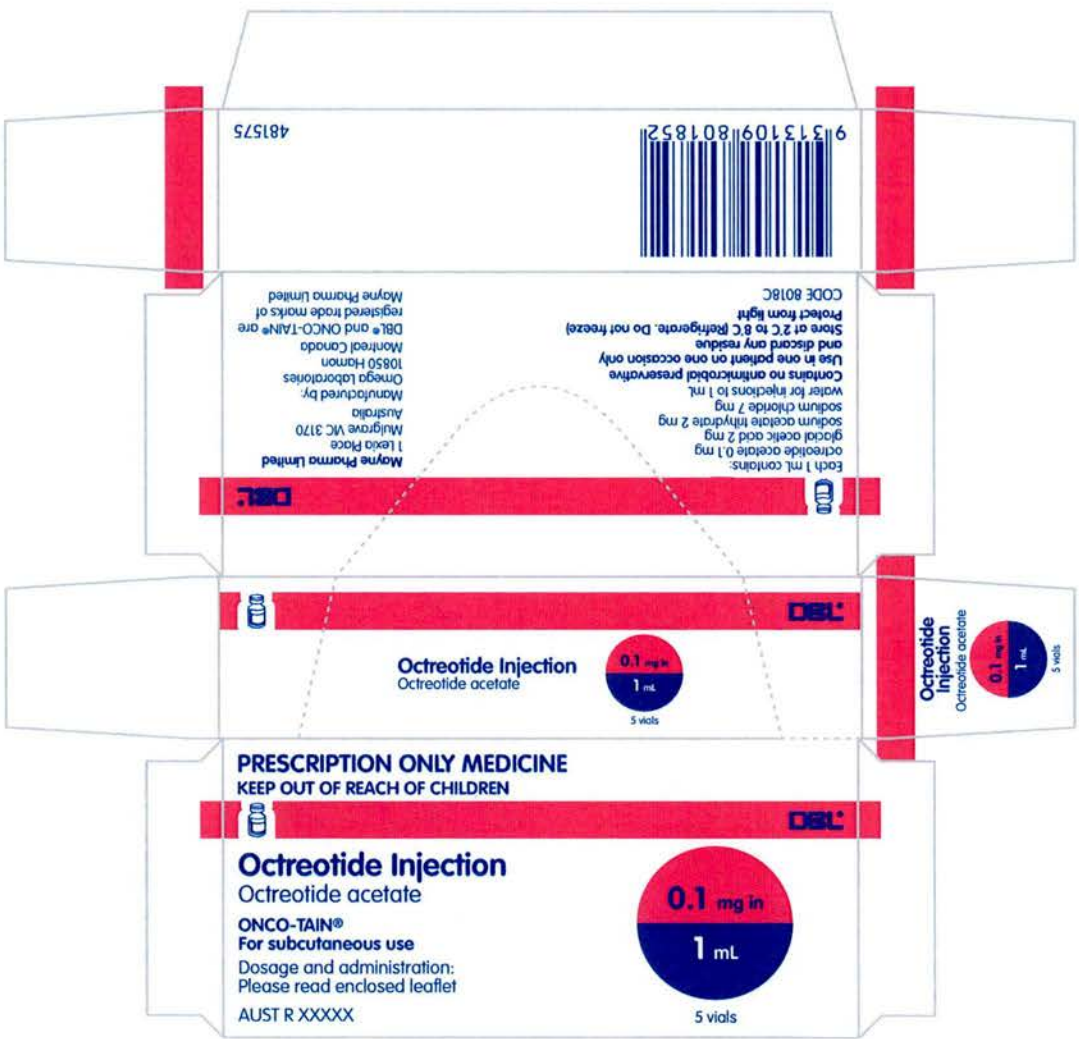
Artworker/Designer	jn



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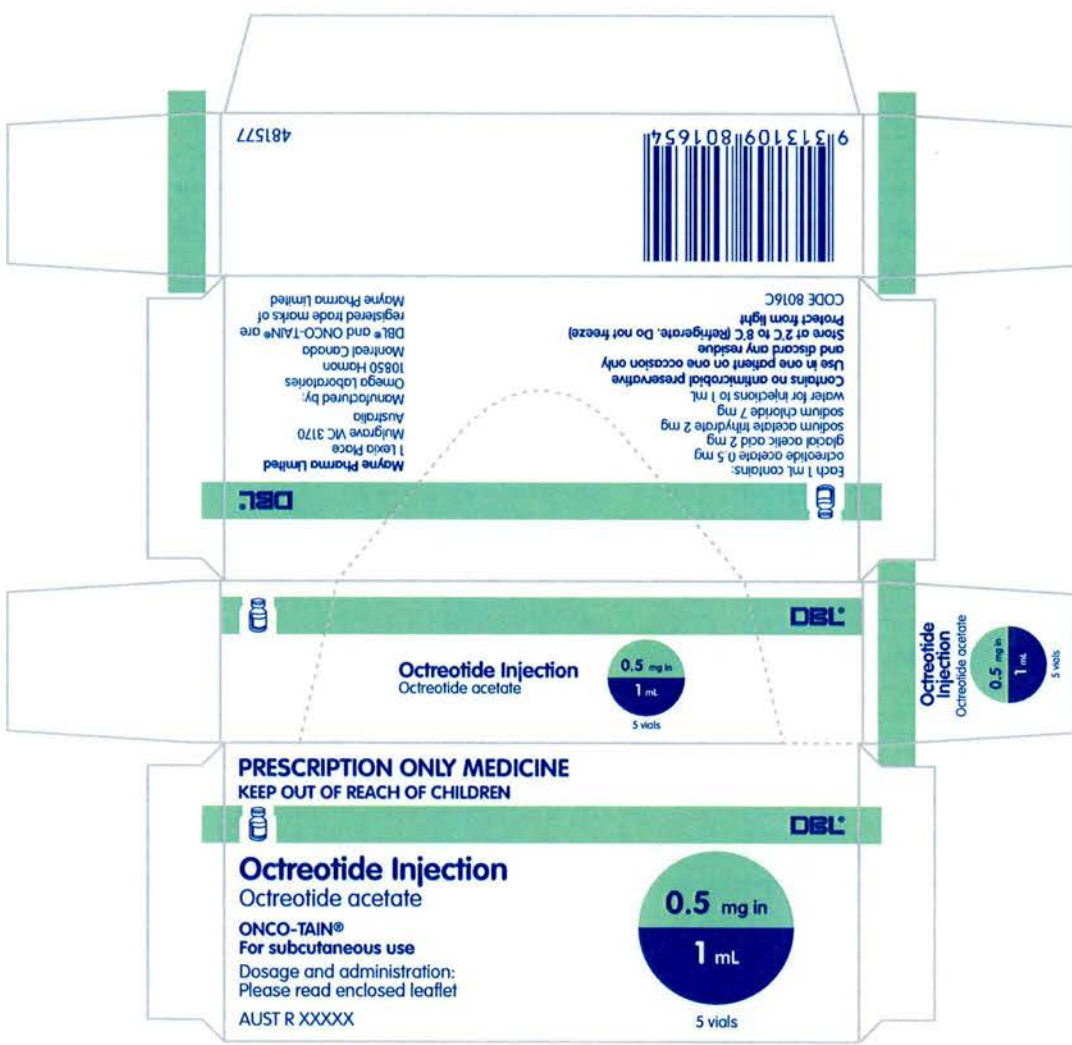

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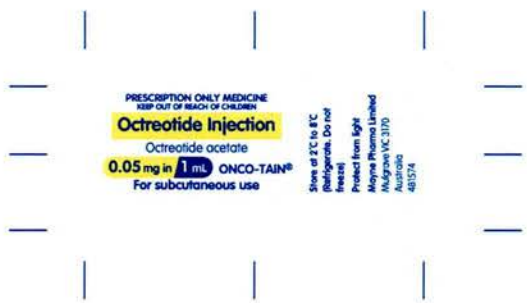

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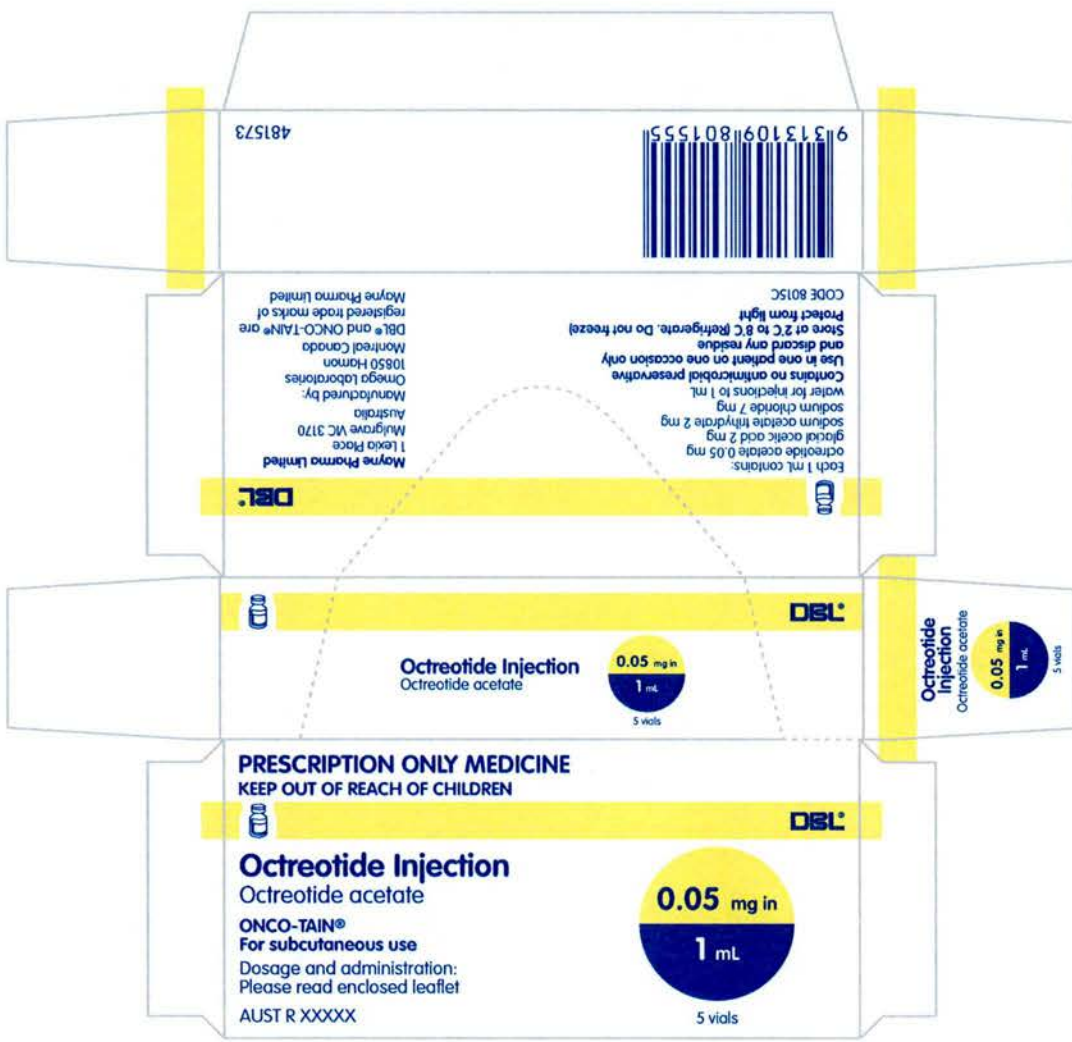

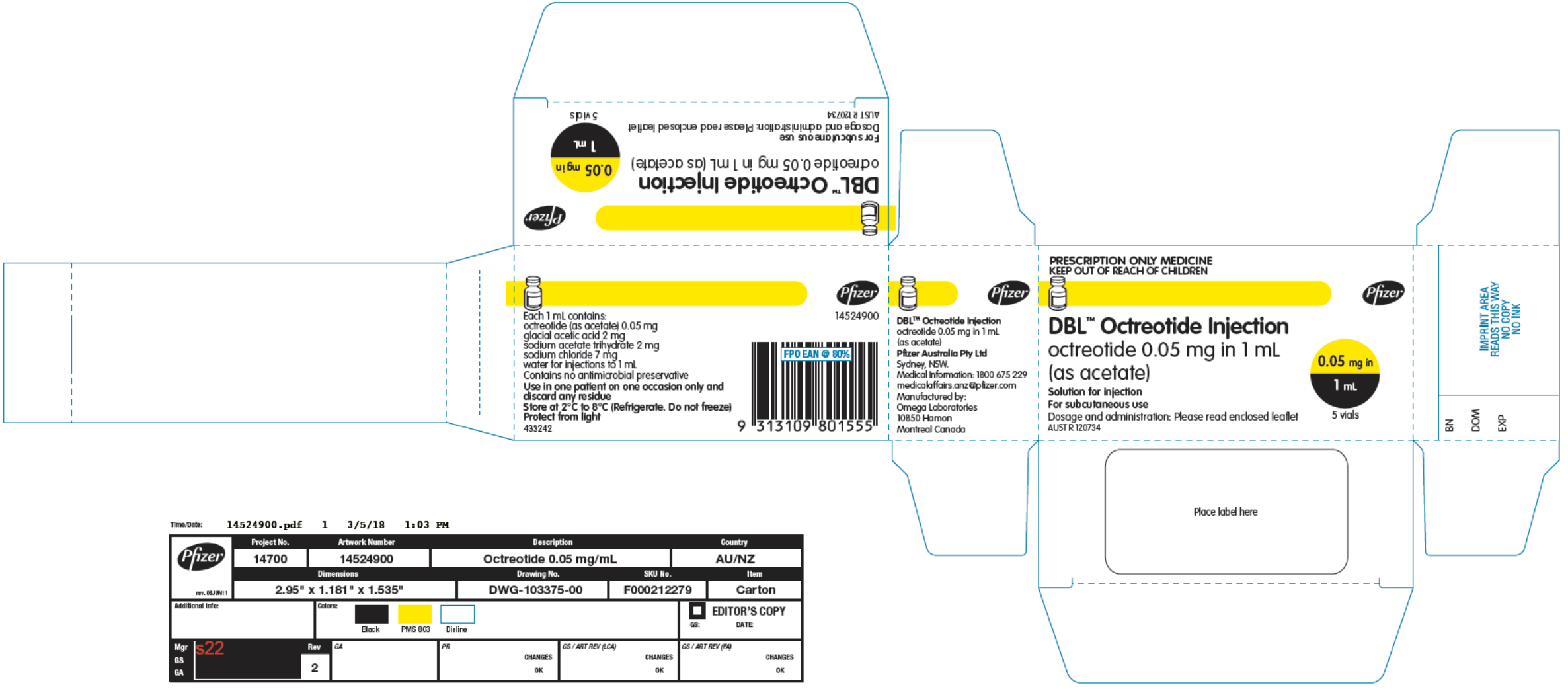

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rev. 08JUN11

Additional Info:

Colors: Black, PMS 803, Dieline

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GS: DATE

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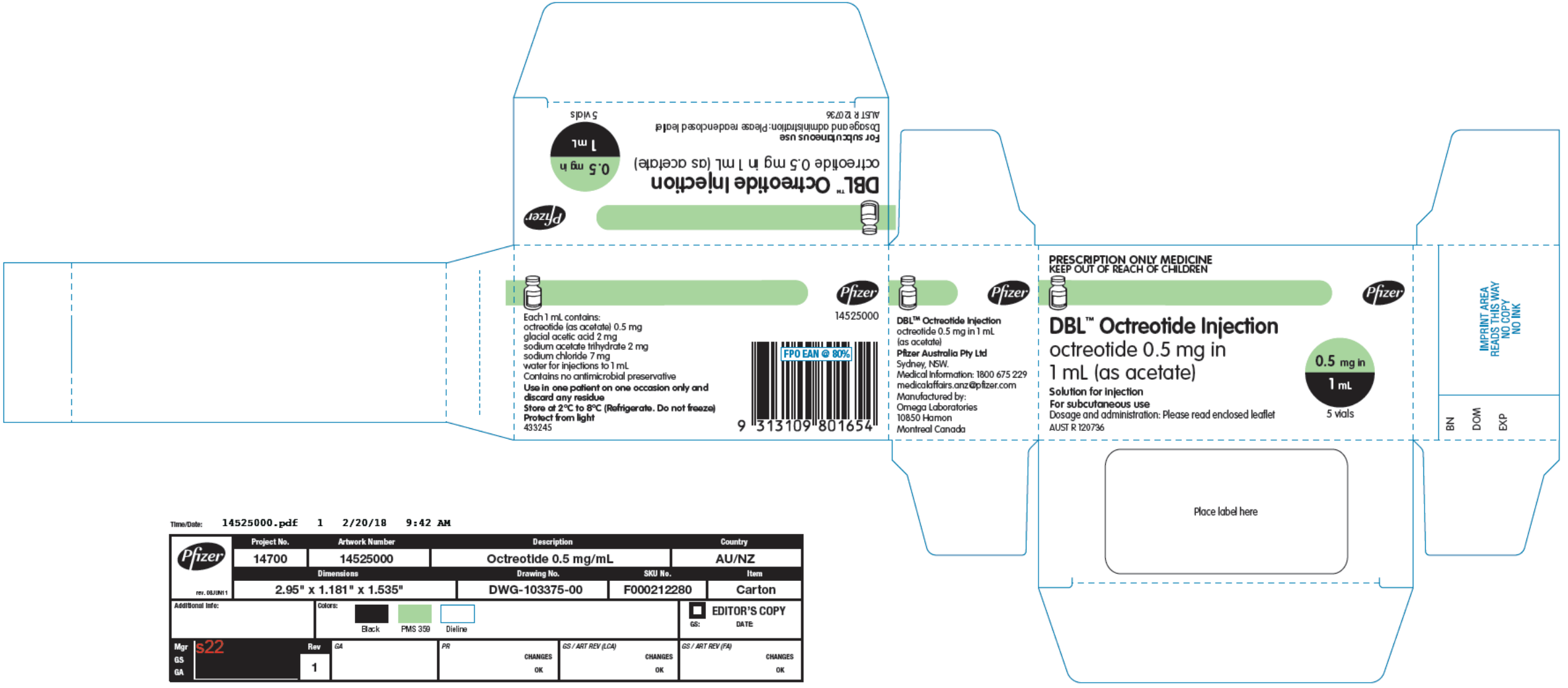

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rev. 08JUN11

Additional Info:

Colors: Black, PMS 359, Dieline

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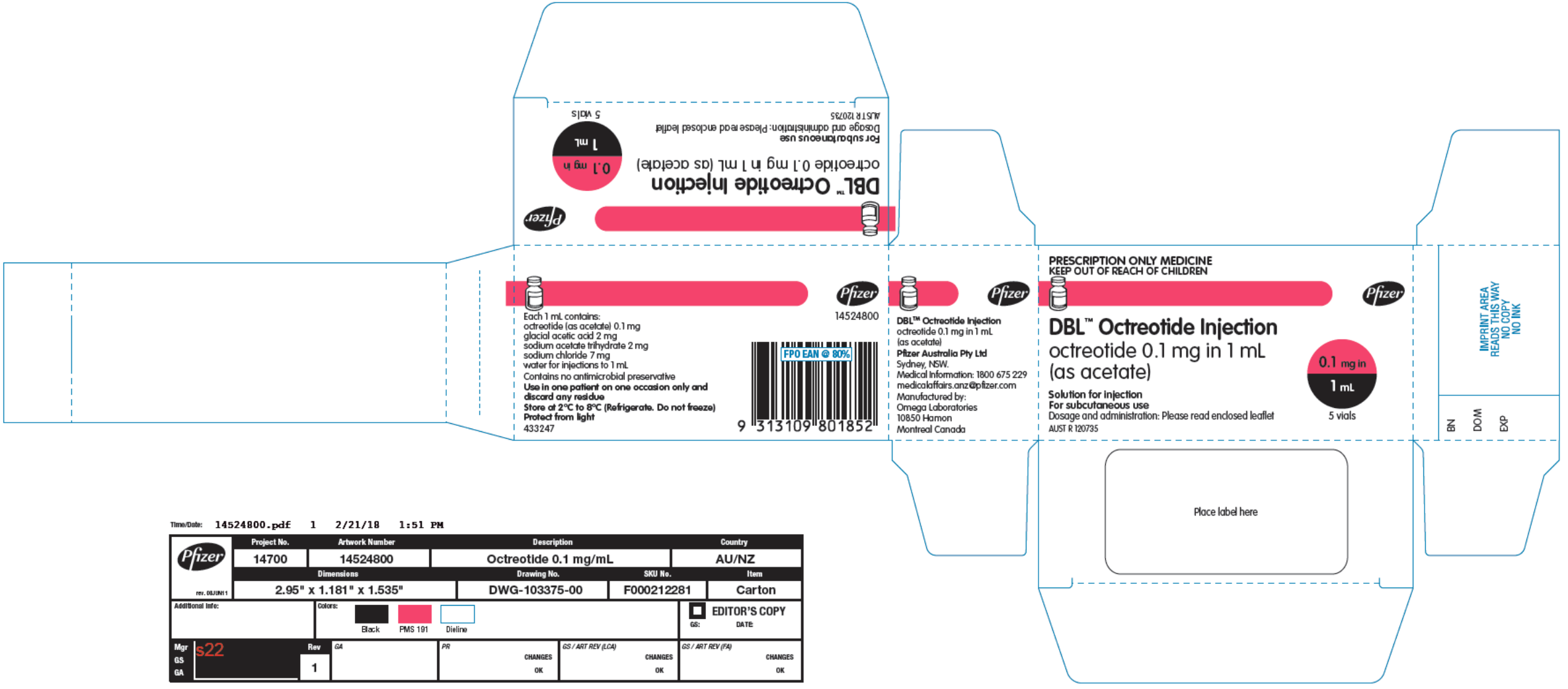

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rev. 08JUN11

Additional Info:

Colors: Black, PMS 191, Dieline

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GS: DATE

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AUSTRALIAN PRODUCT INFORMATION – DBL™ OCTREOTIDE INJECTION (Octreotide)

1. NAME OF THE MEDICINE

Octreotide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

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

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

3. PHARMACEUTICAL FORM

DBL™ Octreotide Injection is a clear colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system:

    - Carcinoid tumours with features of the carcinoid syndrome

    - Vasoactive intestinal peptide secreting tumours (VIPomas).

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

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

4.2 Dose and Method of Administration

Dosage

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 on clinical symptoms and on tolerability. In most patients

the optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with 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, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 mcg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

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

Method of Administration

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

To reduce local discomfort, it is recommended that the solution reaches room temperature before injection. Multiple injections at short intervals at the same site should be avoided. 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 Injection contains no antimicrobial agent. Product is for single use in one patient only. Discard any remaining contents.

Dosage Adjustments

Use in the Elderly

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

Use in Children

Experience with octreotide in children is very limited.

4.3 Contraindications

Hypersensitivity to octreotide or to any component of the formulation.

4.4 Special Warnings and Precautions for Use

Development of gallstones

Development of gallstones has been reported in 15 to 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 to 20%. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

GH secreting pituitary tumours

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

Gastro-entero-pancreatic endocrine tumours

In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Effects on glucose regulation

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

Patients with type I diabetes mellitus requiring insulin therapy may have their insulin requirements reduced by administration of octreotide. In non-diabetic patients and patients with type II diabetes mellitus who have partially intact insulin reserves, octreotide administration can result in prandial increases in glycaemia (see Section 4.8 Adverse effects (undesirable effects)).

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

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

Paediatric use

Experience with octreotide in children is very limited.

Effects on laboratory tests

No data available

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

Octreotide has been reported to produce a reduction in the intestinal absorption of cyclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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, such as insulin, affecting glucose metabolism may be required following initiation of octreotide therapy in patients with diabetes (see Section 4.4 Special warnings and precautions for use: Effects on glucose regulation).

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available

Use in pregnancy – Category C

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.

Reproduction studies have been performed in rats and rabbits at doses up to 1 mg/kg and have revealed no evidence of any adverse effect of octreotide on fertility or morphogenesis. Foetal and post-natal growth retardation was seen in rats, probably due to suppression of growth hormone. No adequate and well controlled studies have been performed in pregnant women. Therefore, this drug should be used in pregnancy only if clearly needed.

Use in lactation

Experience with octreotide in nursing women is not available. In such patients the drug should be used only under compelling circumstances.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Effects (Undesirable Effects)

The main side effects encountered with octreotide administration are local injection site reactions and gastrointestinal effects.

Local reactions

Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness and swelling. They rarely last more than fifteen 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.

Gastrointestinal system

Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea, and steatorrhoea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder

Prolonged use of octreotide may result in gallstone formation (see Section 4.4 Special warnings and precautions for use).

Pancreas

Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation (see Section 4.4 Special warnings and precautions for use) and

impair postprandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been observed.

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

Liver

There have been isolated reports of hepatic or biliary dysfunctions associated with octreotide administration. These consist of the following:

- acute hepatitis without cholestasis where normalisation of transaminase values on withdrawal of octreotide has occurred.

- the slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Body as a whole

Rarely, transient hair loss has been reported. Rare cases of hypersensitivity skin reactions and very rare cases of anaphylactic reactions have been reported. Bradycardia has been reported very rarely.

Other

Other reactions that occur less frequently include headache, dizziness/light-headedness, fatigue, asthenia/weakness, flushing, oedema.

One case of clinical hypothyroidism has been reported in a patient who had received 1500 mcg octreotide daily for 19 months.

Reporting suspected adverse effects

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

4.9 Overdose

Symptoms

No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

Treatment

The management of overdosage is symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). In New Zealand, call 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

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

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

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

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

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

Effects of octreotide in the different tumour types are as follows:

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

- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

Distribution

The distribution of octreotide from plasma was rapid ($t½_{\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the

plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

Excretion

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

The elimination capacity may be reduced in patients with liver cirrhosis (see Section 4.4 Special warnings and precautions for use : use in patients with impaired heaptic function), but not in patients with fatty liver disease.

Effect of renal and hepatic dysfunction on pharmacokinetics:

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

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special Precautions for Storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

6.5 Nature and Contents of Container

DBL™ Octreotide Injection is available as:

0.05 mg/1 mL vial, 5 pack	AUST R 120734
0.1 mg/1 mL vial, 5 pack	AUST R 120735
0.5 mg/1 mL vial, 5 pack	AUST R 120736

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

Chemical structure

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

MW: 1019.3 (free peptide)

CAS number

79517-01-4. (octreotide acetate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
38 – 42 Wharf Road
WEST RYDE NSW 2114
Toll Free Number : 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

20 June 2008

10. DATE OF REVISION

TBD

Summary table of Changes

Section changed	Summary of new information
3	Addition of pharmaceutical form information to align with TGA PI form
8	Deletion of New Zealand sponsor details Update to Australian sponsor details

AUSTRALIAN PRODUCT INFORMATION – DBL™ OCTREOTIDE INJECTION (Octreotide)

1. NAME OF THE MEDICINE

Octreotide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

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

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

3. PHARMACEUTICAL FORM

DBL™ Octreotide Injection is a clear colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system:

    - Carcinoid tumours with features of the carcinoid syndrome

    - Vasoactive intestinal peptide secreting tumours (VIPomas).

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

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

4.2 Dose and Method of Administration

Dosage

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 on clinical symptoms and on tolerability. In most patients the

optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with 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, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 mcg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

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

Method of Administration

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

To reduce local discomfort, it is recommended that the solution reaches room temperature before injection. Multiple injections at short intervals at the same site should be avoided. 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 Injection contains no antimicrobial agent. Product is for single use in one patient only. Discard any remaining contents.

Dosage Adjustments

Use in the Elderly

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

Use in Children

Experience with octreotide in children is very limited.

4.3 Contraindications

Hypersensitivity to octreotide or to any component of the formulation.

4.4 Special Warnings and Precautions for Use

Development of gallstones

Development of gallstones has been reported in 15 to 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 to 20%. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

GH secreting pituitary tumours

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

Gastro-entero-pancreatic endocrine tumours

In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Effects on glucose regulation

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

Patients with type I diabetes mellitus requiring insulin therapy may have their insulin requirements reduced by administration of octreotide. In non-diabetic patients and patients with type II diabetes mellitus who have partially intact insulin reserves, octreotide administration can result in prandial increases in glycaemia (see Section 4.8 Adverse effects (undesirable effects)).

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

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

Paediatric use

Experience with octreotide in children is very limited.

Effects on laboratory tests

No data available

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

Octreotide has been reported to produce a reduction in the intestinal absorption of cyclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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, such as insulin, affecting glucose metabolism may be required following initiation of octreotide therapy in patients with diabetes (see Section 4.4 Special warnings and precautions for use: Effects on glucose regulation).

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available

Use in pregnancy – Category C

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.

Reproduction studies have been performed in rats and rabbits at doses up to 1 mg/kg and have revealed no evidence of any adverse effect of octreotide on fertility or morphogenesis. Foetal and post-natal growth retardation was seen in rats, probably due to suppression of growth hormone. No adequate and well controlled studies have been performed in pregnant women. Therefore, this drug should be used in pregnancy only if clearly needed.

Use in lactation

Experience with octreotide in nursing women is not available. In such patients the drug should be used only under compelling circumstances.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Effects (Undesirable Effects)

The main side effects encountered with octreotide administration are local injection site reactions and gastrointestinal effects.

Local reactions

Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness and swelling. They rarely last more than fifteen 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.

Gastrointestinal system

Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea, and steatorrhoea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder

Prolonged use of octreotide may result in gallstone formation (see Section 4.4 Special warnings and precautions for use).

Pancreas

Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation (see Section 4.4 Special warnings and precautions for use) and

impair postprandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been observed.

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

Liver

There have been isolated reports of hepatic or biliary dysfunctions associated with octreotide administration. These consist of the following:

- acute hepatitis without cholestasis where normalisation of transaminase values on withdrawal of octreotide has occurred.
- the slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Body as a whole

Rarely, transient hair loss has been reported. Rare cases of hypersensitivity skin reactions and very rare cases of anaphylactic reactions have been reported. Bradycardia has been reported very rarely.

Other

Other reactions that occur less frequently include headache, dizziness/light-headedness, fatigue, asthenia/weakness, flushing, oedema.

One case of clinical hypothyroidism has been reported in a patient who had received 1500 mcg octreotide daily for 19 months.

Reporting suspected adverse effects

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

4.9 Overdose

Symptoms

No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

Treatment

The management of overdosage is symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). In New Zealand, call 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

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

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

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

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

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

Effects of octreotide in the different tumour types are as follows:

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

- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

Distribution

The distribution of octreotide from plasma was rapid ($t_{½\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the

plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

Excretion

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

The elimination capacity may be reduced in patients with liver cirrhosis (see Section 4.4 Special warnings and precautions for use : use in patients with impaired heaptic function), but not in patients with fatty liver disease.

Effect of renal and hepatic dysfunction on pharmacokinetics:

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

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special Precautions for Storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

6.5 Nature and Contents of Container

DBL™ Octreotide Injection is available as:

0.05 mg/1 mL vial, 5 pack	AUST R 120734
0.1 mg/1 mL vial, 5 pack	AUST R 120735
0.5 mg/1 mL vial, 5 pack	AUST R 120736

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

Chemical structure

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

MW: 1019.3 (free peptide)

CAS number

79517-01-4. (octreotide acetate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number : 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

20 June 2008

10. DATE OF REVISION

TBA

Summary table of Changes

Section changed	Summary of new information
8	Update to sponsor address

AUSTRALIAN PRODUCT INFORMATION – DBL™ OCTREOTIDE INJECTION (Octreotide acetate) Solution for Injection

1. NAME OF THE MEDICINE

Octreotide acetate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Octreotide Injection contains octreotide (as acetate), a synthetic octapeptide analogue of somatostatin.

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

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

3. PHARMACEUTICAL FORM

Solution for injection.

DBL™ Octreotide Injection is a clear colourless solution free of foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system:

    - Carcinoid tumours with features of the carcinoid syndrome

    - Vasoactive intestinal peptide secreting tumours (VIPomas).

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

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

4.2 Dose and Method of Administration

Dosage

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 on clinical symptoms and on tolerability. In most patients the optimal daily dose will be 0.2 to 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of biochemical markers should be made periodically.

If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within three months of starting treatment with 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, the effect on levels of circulating tumour products, and on tolerability, dosage can be gradually increased to 0.2 mg 3 times daily. Under exceptional circumstances higher doses may be required, however experience with doses above 750 µg per day is limited. Maintenance doses can be variable, depending on differences in tumour activity and rate of progression.

Complications following pancreatic surgery

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

Method of Administration

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

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

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

Development of gallstones has been reported in 15 to 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 to 20%. Cholelithiasis is a very common event during octreotide treatment and may be associated with cholecystitis and biliary tract dilatation (see Section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the post-marketing setting, cases of cholangitis have been reported as a complication of cholelithiasis in patients receiving octreotide. Ultrasonic examination of the gallbladder before and at 6 to 12 monthly intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

GH secreting pituitary tumours

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

Gastro-entero-pancreatic endocrine tumours

In the treatment of gastro-entero-pancreatic endocrine tumours sudden escape from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Effects on glucose regulation

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

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

Oesophageal varices

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

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving ocreotide therapy. Monitoring of vitamin B_{12} levels is recommended during

therapy with DBL™ Octreotide Injection in patients who have a history of vitamin B_{12} deprivation.

Thyroid function

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

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

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

Paediatric use

Experience with octreotide in children is very limited.

Effects on laboratory tests

See subheading Nutrition above.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

Octreotide has been reported to produce a reduction in the intestinal absorption of ciclosporin, and a delay in that of cimetidine.

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

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

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

Where symptoms are severe and octreotide therapy is added to other therapies used to control glycaemic states such as sulphonylureas, insulin, diazoxide, and to beta 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, such as insulin, affecting glucose metabolism may be required following initiation of octreotide therapy in patients with diabetes (see Section 4.4 Special Warnings and Precautions for Use: Effects on glucose regulation).

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

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.

Effects on fertility

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

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.

No adequate and well controlled studies have been performed 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 µg/day of subcutaneous octreotide. 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 Injection should only be prescribed to pregnant women under compelling circumstances.

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

Use in lactation

It is not known whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during treatment with DBL™ Octreotide Injection.

4.7 Effects on Ability to Drive and Use Machines

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

However, adverse effects of this medicine include dizziness and asthenia which could affect the ability to drive or operate machinery (see Section 4.8 Adverse Effects (Undesirable Effects)).

4.8 Adverse Effects (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, flatulaence, 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:	Elevated transaminase levels.
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 and impair post-prandial glucose tolerance. In some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been reported.

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

Post-marketing experience

Adverse drug reactions derived from post-marketing experience with octreotide via spontaneous case reports and literature cases are presented in Table 2. Because these reactions are reported voluntarily from a population of uncertain size it is not possible to reliably estimate frequency. Adverse drug reactions are listed according to SOCs in MedDRA, and are ranked in order of decreasing seriousness within each SOC.

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

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

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

One case of clinical hypothyroidism has been reported in a patient who had received 1500 µg octreotide daily for 19 months.

Description of selected adverse drug reactions

Injection site reactions

Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness, swelling, irritation and rash. They rarely last more than fifteen 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.

Gastrointestinal system

Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has lead to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Gallbladder

Prolonged use of octreotide may result in gallstone formation (see Section 4.4 Special Warnings and Precautions for Use).

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 Special Warnings and Precautions for Use).

Pancreatitis

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

Reporting suspected adverse effects

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

4.9 Overdose

No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1.0 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved within 24 hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (0.25 mg per hour for 48 hours instead of 0.025 mg per hour). He experienced no side effects.

The management of overdosage is symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). In New Zealand, call 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits the secretion of serotonin and the gastro-entero-pancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide, and of growth hormone (GH). Octreotide, like somatostatin, decreases splanchnic blood flow.

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

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

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

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

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

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

Effects of octreotide in the different tumour types are as follows:

- *Carcinoid tumours:* Administration of octreotide may result in improvement of symptoms, particularly of flushing episodes and severe diarrhoea. In some cases this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid. In the event of no beneficial response to octreotide

treatment, continuation of therapy beyond one week at the maximum tolerated dose is not recommended, although in non-responders no serious sustained adverse drug effects have been reported.

- *Vasoactive intestinal peptide secreting tumours (VIPomas):* The biochemical characteristic of these tumours is overproduction of 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.

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).

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

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 µg dose) were reached 0.4 hours after dosing. In a single dose study, the absolute bioavailability after subcutaneous administration was found to be significantly different for different doses, however the interindividual variability was large. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80 to 135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay. Peak concentrations and area under the curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 µg and with multiple doses of 200 µg t.i.d. (600 µg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 µg/day as compared to 150 µg/day. The relative decrease in clearance with doses above 600 µg/day is not defined.

Distribution

The distribution of octreotide from plasma was rapid ($t_{½\alpha}$= 0.2 hours) and the volume of distribution after intravenous dosing was estimated to be 0.27 L/kg body weight. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

Excretion

The elimination of octreotide from plasma had an apparent half-life of 1.5 hours compared with 1 to 3 minutes with the natural hormone. The duration of action of octreotide is variable but

extends up to 12 hours depending upon the type of tumour. About 32% of the dose is excreted unchanged into the urine.

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

Effect of renal and hepatic dysfunction on pharmacokinetics:

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

5.3 Preclinical Safety Data

Genotoxicity

Carcinogenicity

In repeat dose toxicity studies in rats of 52 weeks duration and longer, predominantly in males, sarcomas were noted at the subcutaneous injection site of octreotide in an acidic vehicle and at a lower incidence with the acidic vehicle alone. These did not occur in a mouse carcinogenicity study, nor did hyperplastic or neoplastic lesions occur at the subcutaneous injection site in a 52 week dog toxicity study.

There have been no reports of tumour formation at the injection sites in patients treated for up to 15 years with octreotide. All information available at present indicates that the finding of injection site sarcomas in rats is species-specific and has no significance for the use of the drug in humans.

The 116 week rat carcinogenicity study also revealed uterine endometrial adenocarcinomas, their incidence reaching statistical significance at the highest dose of 1.25 mg/kg per day. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumours were associated with estrogen dominance in the aged female rats which does not occur in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Glacial acetic acid

Sodium acetate trihydrate

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special Precautions for Storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in the original packaging in order to protect from light.

6.5 Nature and Contents of Container

DBL™ Octreotide Injection is available in glass (Type 1 coloured) vials; pack sizes:

0.05 mg/1 mL vial, 5 pack	AUST R 120734
0.1 mg/1 mL vial, 5 pack	AUST R 120735
0.5 mg/1 mL vial, 5 pack	AUST R 120736

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

Chemical structure

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

MW: 1019.3 (free peptide).

CAS number

Octreotide acetate: 79517-01-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number : 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

20 June 2008

10. DATE OF REVISION

ddmmyyyy

Summary table of changes

Section changed	Summary of new information
All	PI reformat/editorial changes
Section 2	Added excipients with known effect.
Section 4.2	Removed duplicated information on the use in the elderly and in children.
Section 4.4	Added information on cardiovascular related events, nutrition and thyroid function. Updated information on gallstones.
Section 4.6	Added information in relation to women of childbearing potential. Added a statement regarding the effect of octreotide on human fertility. Expanded information on the use in pregnancy.
Section 4.8	The most frequent adverse reactions are updated. Added a statement of the most common adverse reactions reported from clinical trials. Added a table of ADRs reported from clinical trials with octreotide ranked by frequency within the MedDRA SOC. ADRs derived from post-marketing experience are listed according to SOCs in MedDRA, ranked in order of decreasing seriousness within each SOC. Newly listed ADRs: dyspnoea, tachycardia, endocrine disorders, dehydration, elevated transaminase levels, arrhythmias, Blood alkaline phosphatase increased, gamma glutamyl transferase increased. Added information on cardiac disorders.
Section 5.1	Added pharmacotherapeutic group.
Section 6.4	Added recommendation to store in the original packaging in order to protect from light.


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Octreotide Injection
Octreotide (as acetate)
0.05 mg in 1 mL
For subcutaneous use
Store at 2˚C to 8˚C
(Refrigerate. Do not freeze)
Protect from light
Mayne Pharma Limited
Mulgrave VIC 3170
Australia
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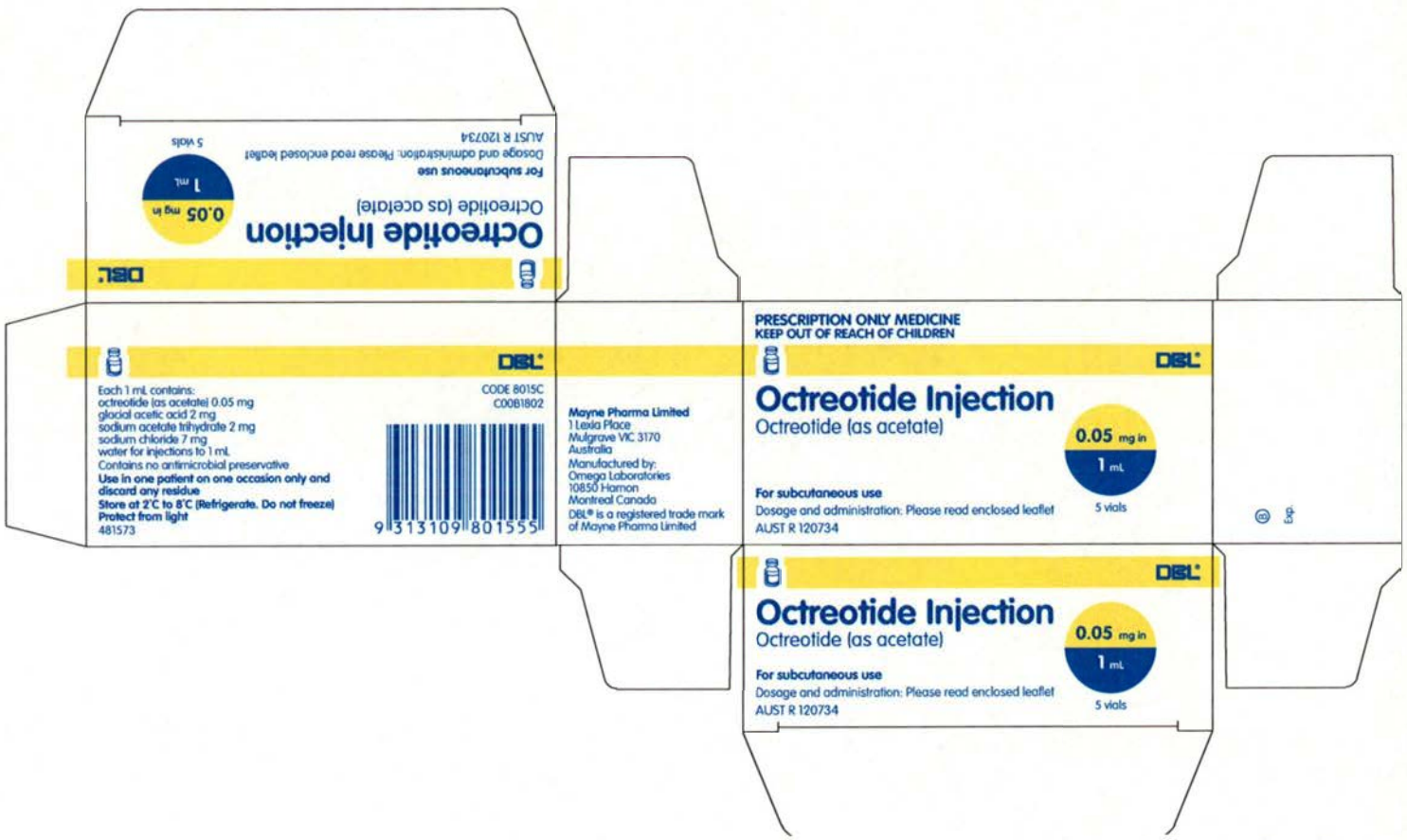
Exp.


Octreotide Injection
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0.05 mg in 1 mL
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Dosage and administration: Please read enclosed leaflet
AUST R 120734
5 vials
DBL
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For subcutaneous use
Dosage and administration: Please read enclosed leaflet
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5 vials
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Each 1 mL contains:
octreotide (as acetate) 0.05 mg
glacial acetic acid 2 mg
sodium acetate trihydrate 2 mg
sodium chloride 7 mg
water for injections to 1 mL
Contains no antimicrobial preservative
Use in one patient on one occasion only and discard any residue
Store at 2°C to 8°C (Refrigerate. Do not freeze)
Protect from light
481573
CODE 8015C
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9 313109 801555
Mayne Pharma Limited
1 Lexia Place
Mulgrave VIC 3170
Australia
Manufactured by:
Omega Laboratories
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Montreal Canada
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Australia
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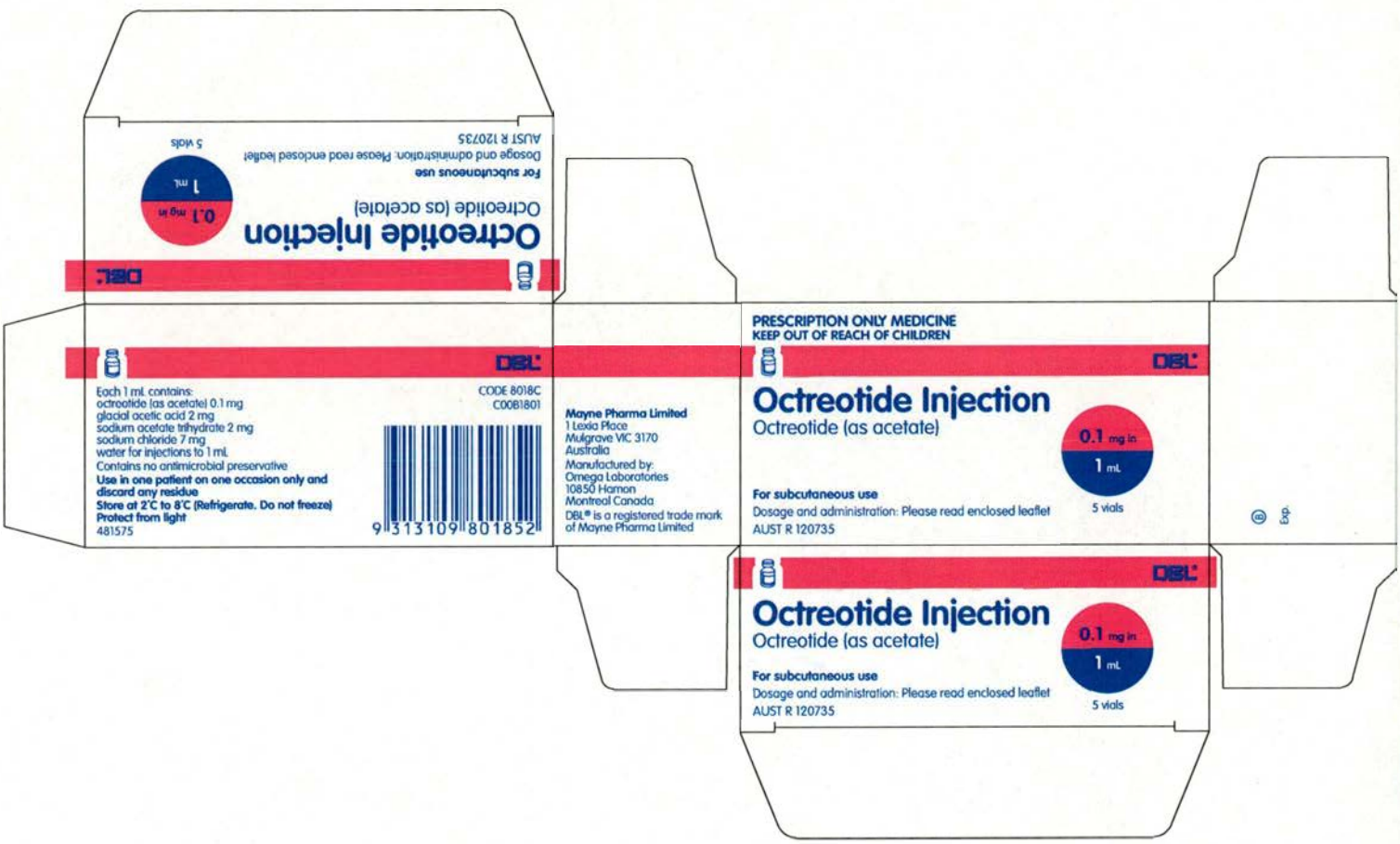
Octreotide Injection
Octreotide (as acetate)
0.1 mg in 1 mL
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AUST R 120735
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DBL
Each 1 mL contains:
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glacial acetic acid 2 mg
sodium acetate trihydrate 2 mg
sodium chloride 7 mg
water for injections to 1 mL
Contains no antimicrobial preservative
Use in one patient on one occasion only and discard any residue
Store at 2°C to 8°C (Refrigerate. Do not freeze)
Protect from light
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CODE 8018C
C00B1801
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PRESCRIPTION ONLY MEDICINE
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Octreotide Injection

Octreotide (as acetate)

0.5 mg in 1 mL

For subcutaneous use

Store at 2°C to 8°C
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Protect from light

Mayne Pharma Limited
Mulgrave VIC 3170
Australia
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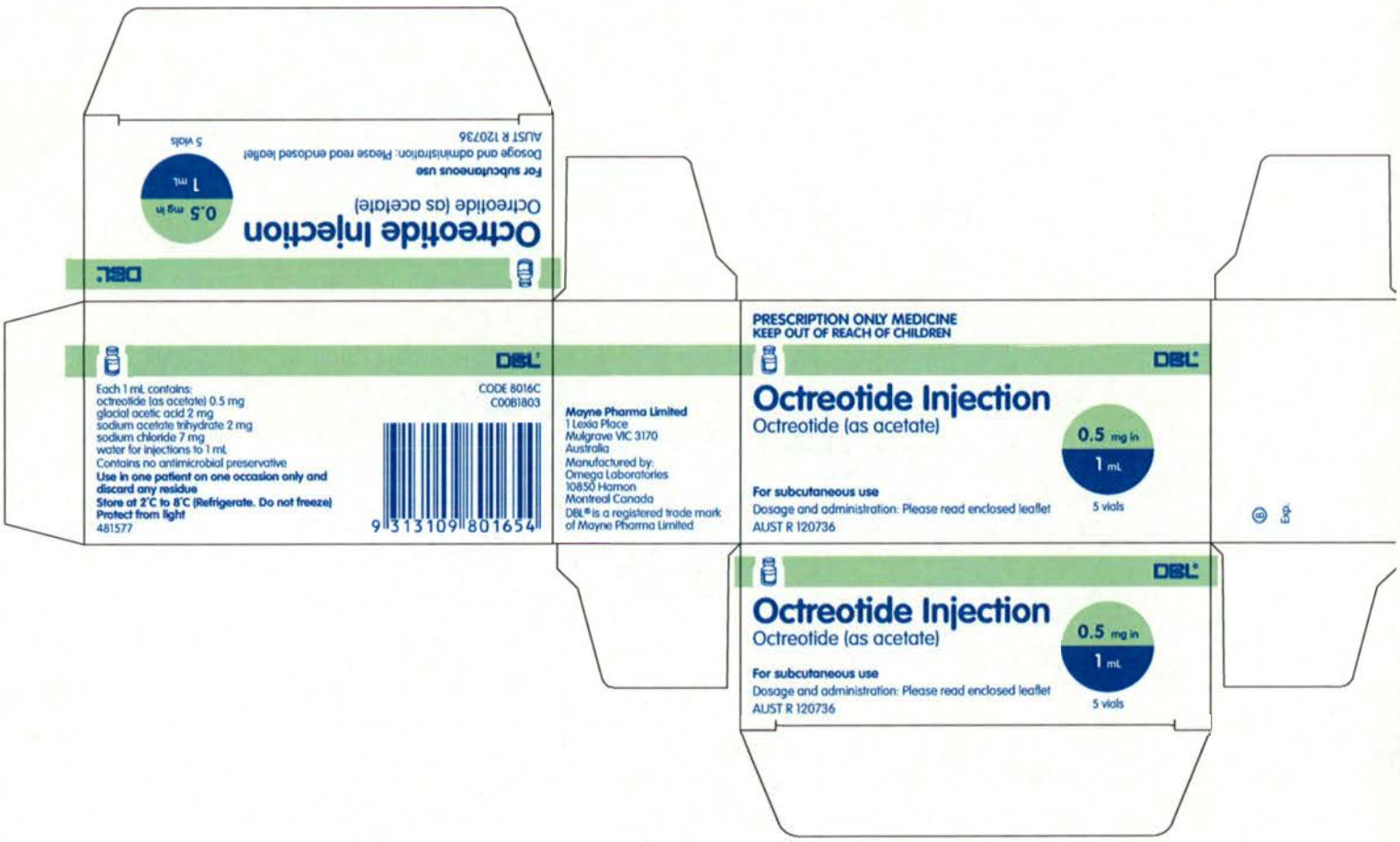
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