PRODUCT MONOGRAPH

INCLUDING **PATIENT MEDICATION INFORMATION**

[Pr]Octreotide Acetate Injection

Octreotide acetate injection
50 mcg/mL, 100 mcg/mL, 500 mcg/mL Solution for Subcutaneous injection or Intravenous infusion

Synthetic octapeptide analogue of somatostatin (H01CB02)

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Carcinoid Tumours	11/2021
7 WARNINGS AND PRECAUTIONS, Fertility	11/2021
7 WARNINGS AND PRECAUTIONS, Teratogenic Risk	11/2021
7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	11/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Octreotide Acetate Injection Solution for injection or infusion

General

Octreotide Acetate Injection (octreotide acetate) therapy is indicated for control of symptoms in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumours (VIPomas) as well as in patients with acromegaly.

Data are insufficient to determine whether octreotide acetate decreases the size, rate of growth, or development of metastases in patients with these tumours.

Octreotide Acetate Injection is also indicated for the prevention of complications following pancreatic surgery in patients undergoing high risk procedures.

Octreotide Acetate Injection is also indicated for the emergency management of bleeding gastro-oesophageal varices in patients with cirrhosis and as protection from re-bleeding. Octreotide Acetate Injection is used in association with specific intervention such as endoscopic sclerotherapy.

Carcinoid Tumours

Octreotide Acetate Injection is indicated for the symptomatic treatment of metastatic carcinoid tumours where it suppresses or inhibits the severe diarrhoea and flushing episodes associated with the disease.

Vasoactive Intestinal Peptide Tumours (VIPomas)

Octreotide Acetate Injection is indicated for the treatment of the profuse watery diarrhoea associated with VIP-secreting tumours. Significant improvement has been noted in the overall condition of these otherwise therapeutically unresponsive patients. Therapy with octreotide acetate results in improvement in electrolyte abnormalities, e.g., hypokalaemia, often enabling reduction of fluid and electrolyte support.

Acromegaly

Octreotide Acetate Injection is indicated to reduce blood levels of growth hormone and IGF-1 (somatomedin C) including acromegalic patients who have had inadequate response to, or cannot be treated with surgical resection, pituitary irradiation and/or bromocriptine mesylate at maximally tolerated doses.

Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with Octreotide Acetate Injection to reduce blood levels of GH and IGF-1 offers potential benefit before the effects of irradiation are manifested.

A clinically relevant growth hormone (GH) reduction (by 50% or more) occurs in almost all patients, and normalisation (plasma GH < 5 mcg/L) can be achieved in about half of the cases.

In most patients, octreotide acetate markedly reduces the clinical symptoms of the disease such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paraesthesia. In patients with a large pituitary adenoma, octreotide acetate treatment may result in some shrinkage of the tumour mass.

Prevention of Complications following Pancreatic Surgery

Octreotide Acetate Injection inhibits basal and stimulated exocrine pancreatic secretion and when administered peri- and post-operatively in patients undergoing high risk pancreatic surgery, reduces the incidence and severity of typical post-operative complications (e.g. pancreatic fistula, abscess and subsequent sepsis and post-operative acute pancreatitis).

Bleeding Gastro-oesophageal Varices

In patients presenting with bleeding gastro-oesophageal varices due to underlying cirrhosis, Octreotide Acetate Injection administration in combination with specific intervention (e.g. sclerotherapy) provides better control of bleeding and early rebleeding, reduces transfusion requirements and improves 5-day survival).

1.1 Pediatrics

Paediatrics (between birth and 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for paediatric use (see **7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics**).

1.2 Geriatrics

Information specific to the geriatric population is not available for this drug product.

2 CONTRAINDICATIONS

Octreotide Acetate Injection (octreotide acetate) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Octreotide Acetate Injection Solution for injection s.c. Ampoules

Subcutaneous injection is the recommended route of administration of Octreotide Acetate Injection (octreotide acetate) for control of symptoms in most instances. Intravenous bolus injections have been used under emergency conditions. Multiple injections at the same site within short periods of time should be avoided. The initial dosage is 50 mcg, administered subcutaneously, once or twice daily. Thereafter, the number of injections and dosage may be increased gradually based on patient tolerability, clinical response and effects on levels of tumour-produced hormones (in cases of carcinoid tumours on the urinary excretion of 5-hydroxyindole-acetic acid). Dosage information for patients with specific tumours is listed below. The drug is usually given in a b.i.d or t.i.d schedule.

- **Carcinoid Tumours**

The suggested daily dosage of Octreotide Acetate Injection during the first two weeks of therapy ranges from 100 to 600 mcg per day in two to four divided doses (mean daily dosage is 300 mcg). In the clinical studies, the median daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1500 mcg per day. However, experience with doses above 750 mcg per day is limited. In the event of no beneficial response to Octreotide Acetate Injection treatment, continuation of therapy beyond one week is not recommended.

- **VIPomas**

Daily dosages of 200 to 300 mcg in two to four divided doses are recommended during the initial 2 weeks of therapy (range 150 to 750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg per day are not required.

- **Acromegaly**

Daily dosages of 100 to 300 mcg b.i.d. or t.i.d. are recommended at the beginning of treatment. Dosage adjustment should be based on monthly assessment of GH levels, insulin-like growth factor 1 (IGF 1) / somatomedin C concentrations and clinical symptoms, and on tolerability. In most patients, the optimal daily dose will be 200 to 300 mcg per day. A maximum dose of 1500 mcg should not be exceeded.

If no relevant reduction of GH and IGF 1 levels and no improvement of clinical symptoms have been achieved within 3 months of starting treatment with Octreotide Acetate Injection, therapy should be discontinued (see **7 WARNINGS AND PRECAUTIONS Monitoring and Laboratory Tests**).

- **Prevention of Complications following Pancreatic Surgery**

Daily dosage of 100 mcg t.i.d., administered subcutaneously, for 7 consecutive days starting on the day of the operation at least one hour before laparatomy.

- **Bleeding Gastro-oesophageal Varices in patients with cirrhosis**

The recommended dose of Octreotide Acetate Injection is 25 mcg/hour by continuous intravenous infusion for 48 hours. In patients with high risk of re-bleeding, infusion should be maintained up to a maximum of 5 days.

Immediately prior to use, the contents of the ampoule should be diluted in physiological saline. The volume of dilution will depend on the infusion system used and should be adjusted to ensure a continuous infusion of Octreotide Acetate Injection at the recommended rate. Once diluted, the solution should be used within 24 hours. Discard unused portion.

As with all parenteral drugs, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.

4.3 Reconstitution

Parenteral Products:

Solution for continuous i.v. infusion: Immediately prior to use, the contents of the ampoule should be diluted in physiological saline. The volume of dilution will depend on the infusion system used and should be adjusted to ensure a continuous infusion of Octreotide Acetate Injection at a rate of 25 mcg/hour. The following are examples of dilutions which may be used:

Octreotide Acetate Injection			Volume of physiological saline	Approximate available volume mL	Nominal concentration mcg/mL	Infusion rate mL/h (mcg/h)
Concentration mcg/mL	Size mL	Volume mL				
500	1	1	49	50	10	2.5 (25)
500	1	1	79	80	6.25	4 (25)
100	1	1	15	16	6.25	4 (25)

As with all parenteral drugs, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.

Octreotide Acetate Injection diluted in physiological saline is stable for 24 hours when stored at room temperature. Discard unused portion.

Octreotide acetate is not stable in Total Parenteral Nutrition (TPN) solutions. It is generally not recommended to mix other medicinal products with octreotide in the same infusion bag or in the same cannula. Physical incompatibilities have been reported (e.g. with pantoprazole).

4.5 Missed Dose

Octreotide Acetate Injection Solution for injection or infusion
If an injection is missed, the dose should not be doubled at the next injection.

5 OVERDOSAGE

Octreotide acetate Solution for injection or infusion s.c. Ampoules

A limited number of accidental overdoses of octreotide acetate in adults and children have been reported. In adults, the doses ranged from 2,400-6,000 mcg/day administered by continuous infusion (100-250 mcg/hour) or subcutaneously (1,500 mcg t.i.d.). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis. Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving higher doses of continuous infusion (100 mcg/hr) and/or bolus of octreotide acetate intravenously (50 mcg bolus) followed by 50 mcg/hr continuous infusion).

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

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

The management of overdosage is symptomatic.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	**Dosage Form / Strength / Composition**	**Non-medicinal Ingredients**
Subcutaneous injection and intravenous infusion	Single dose ampoule (1 mL)	
	Solution: 50 mcg/mL, 100 mcg/mL and 500 mcg/mL octreotide (free peptide) (present as octreotide acetate)	lactic acid: 3,600 mcg/mL mannitol: 45,000 mcg/mL water for injection: q.s. 1.0 mL
Sodium bicarbonate is added to provide a buffered solution pH 3.2 – 4.2		

Octreotide Acetate Injection
Octreotide Acetate Injection (octreotide acetate) is supplied in 1 mL ampoules, each containing 50, 100 or 500 mcg of octreotide as acetate. Octreotide Acetate Injection is available in boxes of 5 ampoules.

7 WARNINGS AND PRECAUTIONS

General

Sudden escape from symptomatic control by Octreotide Acetate Injection (octreotide acetate) may occur infrequently, with rapid recurrence of severe symptoms. Dosage adjustment therefore may be required.

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

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycaemia or hyperglycaemia. Octreotide also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with octreotide.

Careful instruction in sterile subcutaneous injection techniques should be given to the patients and to other persons who may administer Octreotide Acetate Injection (see **PATIENT**

MEDICATION INFORMATION).

Patients with carcinoid tumours and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

Carcinogenesis and Mutagenesis

Studies in laboratory animals have demonstrated no mutagenic potential of octreotide acetate.

Cardiovascular

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. In one acromegalic patient with severe congestive heart failure, initiation of octreotide acetate injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive re-challenge (see **8 ADVERSE REACTIONS**).

Endocrine and Metabolism

- **Glucose Metabolism**

Octreotide acetate therapy is occasionally associated with mild transient hypo- or hyperglycaemia but may also result in overt diabetes due to alterations in the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone. Patients should be closely observed on introduction of Octreotide Acetate Injection therapy and at each change of dosage for symptomatic evidence of hyper- and hypoglycaemia. Insulin requirement of patients with type I diabetes mellitus may be reduced by administration of octreotide acetate. In non-diabetics and type II diabetics with partially intact insulin reserves, octreotide acetate administration can result in prandial increases in glycaemia. Severe hyperglycaemia, subsequent pneumonia, and death following initiation of octreotide acetate injection therapy was reported in one patient with no history of hyperglycaemia.

Predicting the effect of octreotide acetate on glucose tolerance in any given patient is not possible at this time. It is recommended that all acromegalic patients have their serum glucose carefully monitored during initiation and titration of therapy with Octreotide Acetate Injection s.c.

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

It is therefore recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with Octreotide Acetate Injection s.c.

- **Thyroid Function**

Data on the effect of chronic therapy with octreotide acetate on hypothalamic/pituitary function have not been obtained. A progressive drop in T_4 levels has been reported, culminating in clinical and biochemical hypothyroidism after 19 months of therapy in one clinical trial patient (carcinoid) receiving 1500 mcg of octreotide acetate s.c. daily. Therefore, baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) should be monitored during chronic therapy with octreotide acetate.

Gastrointestinal

- **Nutrition**

There is evidence that octreotide acetate therapy may alter absorption of dietary fats in some patients. It is suggested that periodic quantitative 72-hour faecal fat and serum carotene determinations be performed to aid in the assessment of possible drug-induced aggravation of fat malabsorption.

Depressed vitamin B12 levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

Hepatic/Biliary/Pancreatic

- **Gallbladder and Related Events**

Single doses of octreotide acetate injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with octreotide acetate injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received octreotide acetate injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during octreotide acetate injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy. Additionally, there have been post-marketing reports of cholelithiasis (gallstones) resulting in complications including cholecystitis, cholangitis, pancreatitis, and requiring cholecystectomy in patients taking octreotide acetate.

It is recommended that patients on extended therapy with Octreotide Acetate Injection be evaluated at baseline and periodically (at about 6-month intervals) to assess the presence of

gallstones using ultrasound evaluations of the gallbladder and bile ducts (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**). If complications of cholelithiasis are suspected, discontinue Octreotide Acetate Injection and treat appropriately.

- **Liver Impairment**

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

Monitoring and Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumour. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Acromegaly: Growth hormone - IGF-1 (somatomedin C)

Responsiveness to octreotide may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours after subcutaneous injection of Octreotide Acetate Injection. Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of Octreotide Acetate Injection or dosage change.

In patients with acromegaly, if no relevant reduction of GH and IGF 1 levels and no improvement of clinical symptoms have been achieved within 3 months of starting treatment with Octreotide Acetate Injection, therapy should be discontinued.

Patients should undergo a baseline ultrasound examination of the gallbladder and bile ducts prior to commencing Octreotide Acetate Injection treatment. Periodic ultrasound examination of the gallbladder should be performed, at about 6-month intervals, throughout Octreotide Acetate Injection treatment (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Gallbladder and Related Events**). If stones are already present before the start of therapy, the potential benefit of Octreotide Acetate Injection should be assessed against the potential risks associated with the gallstones. In case of asymptomatic gallstone, Octreotide Acetate Injection may be continued, depending on re-assessment of the benefit/risk ratio with increased frequency of monitoring. Symptomatic gallstones should receive medical attention and be treated.

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy (see **Endocrine and Metabolism, Thyroid Function**).

Renal

- **Renal Impairment**

In patients with severe renal failure requiring dialysis, the half-life of the drug may be increased, necessitating adjustment of the maintenance dosage.

Reproductive Health: Female and Male Potential

- **Fertility**

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients could potentially restore fertility. Pregnancy in acromegalic patients may increase the risk of gestational diabetes, hypertension and exacerbation of the underlying cardiac disease, therefore female patients of childbearing potential should be advised to use adequate contraception during treatment with octreotide.

Animal studies in rats and rabbits did not adversely affect reproduction performance following treatment with Octreotide Acetate Injection at doses up to 1 mg/kg/day (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**).

- **Teratogenic Risk**

There is no direct indication of a teratogenic potential following octreotide acetate treatment in animal studies (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology**).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience, data on a limited number of pregnancies have been reported in patients on octreotide therapy.

7.1.2 Breast-feeding

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 Octreotide Acetate Injection treatment.

7.1.3 Pediatrics

Experience with octreotide acetate s.c. in the paediatric population is limited.

Octreotide acetate injection has been primarily used in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal-steatorrhea, diarrhoea, vomiting and abdominal distension. Poor growth has been reported in several patients treated with octreotide acetate injection for more than 1 year; catch-up growth occurred after octreotide acetate injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of octreotide acetate injection.

7.1.4 Geriatrics

Clinical studies of ocreotide acetate s.c did not include sufficient numbers of patients age 65 years and over to determine whether they respond differently from younger patients. Other

reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent adverse reactions reported with octreotide acetate include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Octreotide acetate s.c. ampoules in GEP and Acromegaly:

Table 1 Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumour Patients and 114 Acromegalic Patients Treated with octreotide acetate

Adverse Reaction Profile According to Body System	GEP Endocrine Tumour Patients (n=196) %	Acromegalic Patients (n=114) %
Gastrointestinal		
Diarrhea	6.6	57.9
Abdominal discomfort	4.1	43.9
Stools Loose	3.1	36.0
Nausea	8.7	29.8
Flatulence	0.5	13.2
Constipation	1.0	8.8
Abdominal distention	-	7.9
Stools abnormal	0.5	6.1
Cholelithiasis	<1.0	4.4
Rectal gas	-	4.4
Vomiting	2.6	4.4
Fatty stools	3.6	-
GI bleeding	0.5	-
Rectal disorders	0.5	-
Hemorrhoids	-	1.8
Cholecystitis	-	1.8
Eructations	-	1.8
Integumentary		
Pain at injection site	8.2	9.6

Adverse Reaction Profile According to Body System	GEP Endocrine Tumour Patients (n=196) %	Acromegalic Patients (n=114) %
Acne	-	4.4
Bruise	0.5	4.4
Pruritus	-	4.4
Alopecia/Baldness/Hair loss	1.0	3.5
Musculoskeletal		
Backache/pain	0.5	4.4
Joint pain	-	4.4
Arthritis	-	2.6
Arm/leg heavy - tired	-	2.6
Leg ache/pain	-	2.6
Osteoarthritis	-	1.8
Vertebral disk disorder	-	1.8
Twitching	-	1.8
Respiratory		
Throat pain	0.5	2.6
Flu symptoms	-	6.1
Cold symptoms	-	6.1
Sinusitis	-	3.5
Nasal congestion	-	1.8
Cardiovascular		
Leg cramps	-	3.5
Dyspnea	-	1.8
Epistaxis	-	1.8
Chest pain	0.5	-
Edema	1.0	2.6
Ischemic Attack	0.5	-
Hypertension	0.5	-
Thrombophlebitis	0.5	-
Cramps	-	2.6
Autonomic		
Visual disturbances	0.5	2.6
Mouth dry/furry/xerostomia	0.5	1.8
Flushing	0.5	1.8
Numbness	-	1.8
Hot flash	-	1.8
Central Nervous		
Headache	1.5	18.4
Dizziness	1.5	14.9
Fatigue	1.0	9.6
Anxiety/Nervousness	0.5	2.6
Asthenia	0.5	-
Bell's palsy	0.5	-
Seizure	0.5	-
Depression	0.5	2.6
Sleepiness/insomnia	0.5	1.8
Weakness	1.0	-
Moody	-	2.6

Adverse Reaction Profile According to Body System	GEP Endocrine Tumour Patients (n=196) %	Acromegalic Patients (n=114) %
Appetite loss	-	1.8
Irritability	-	1.8
Tinnitus	-	1.8
Urogenital		
Urinary tract infection	-	6.1
Pollakiuria	-	3.5
Vagina infection	-	2.6
Vagina itch	-	1.8
Breast lump Dysuria	-	1.8
Kidneys, pain in	-	1.8
Polyuria	-	1.8
Prostatitis	-	1.8
Tumor breast	-	1.8
	-	1.8
Hematologic		
Hematoma, injection site	-	9.6
Endocrine Hypoadrenalism		
Hypothyroidism	-	2.6
Hypogonadism	-	1.8
Hypoglycemia	-	1.8
	-	1.8
Miscellaneous		
Foot pain	-	1.8
Fever	-	1.8
Otitis	-	1.8
Weight gain	-	1.8

Local reactions after s.c. administration of octreotide acetate include pain and sensations of stinging, tingling or burning at the site of injection, with redness and swelling. These rarely last more than fifteen minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection and by slowly injecting octreotide acetate.

In clinical trials, acromegalic patients had a higher incidence of diarrhoea, abdominal pain/discomfort, nausea and loose stools than patients treated with octreotide acetate s.c. for other indications. It is believed that the primary reason for this observation is that patients who received octreotide acetate s.c. for carcinoid syndrome, VIPoma and other gastro -entero-pancreatic tumours had these gastrointestinal symptoms at baseline and would only report them as adverse events if they became more frequent or severe during octreotide acetate s.c. treatment.

The adverse event rate for octreotide acetate during study B301 is presented in comparison to placebo. This comparison more accurately reflects the difference in adverse event rates between octreotide acetate and placebo.

Table 2 Number % Patients in US Studies B301, B302, B303 with Adverse Events by Treatment and by Body System. Events occurring in ≥ 3%

Specific Adverse Event by Body System	Placebo B301 (n=55)%	octreotide acetate B301 (n=60)%	octreotide acetate B301, B302 & B303 (n=114)%
Skin			
Pain at injection site	2 (3.6)	5 (8.3)	11 (9.6)
Acne	--	2 (3.3)	5 (4.4)
Bruise	1 (1.1)	2 (3.3)	5 (4.4)
Pruritus	--	--	5 (4.4)
Alopecia/Baldness/Hair loss	--	--	4 (3.5)
Musculoskeletal			
Back ache/pain	--	--	5 (4.4)
Joint pain	2 (3.6)	1 (1.7)	5 (4.4)
Respiratory			
Flu symptoms	--	2 (3.3)	7 (6.1)
Cold symptoms	--	2 (3.3)	7 (6.1)
Sinusitis	--	--	4 (3.5)
Cardiovascular			
Leg cramps	--	--	4 (3.5)
Hematologic			
Hematoma, injection site	6 (10.9)	1 (1.7)	11 (9.6)
Gastrointestinal			
Diarrhea	6 (10.9)	32 (53.3)	66 (57.9)
Abdominal discomfort	7 (12.7)	14 (23.3)	50 (43.9)
Stools Loose	8 (14.5)	16 (26.7)	41 (36.0)
Nausea	6 (10.9)	17 (28.3)	34 (29.8)
Flatulence	2 (3.6)	6 (10.0)	15 (13.2)
Constipation	--	1 (1.7)	10 (8.8)
Abdominal distention	--	2 (3.3)	9 (7.9)
Stools abnormal	--	3 (5.0)	7 (6.1)
Cholelithiasis	--	--	5 (4.4)
Rectal gas	--	--	5 (4.4)
Vomiting	1 (1.8)	3 (5.0)	5 (4.4)
Urogenital			
Urinary tract infection	--	3 (5.0)	7 (6.1)
Pollakiuria	2 (3.6)	1 (1.7)	4 (3.5)
Central Nervous			
Headache	6 (10.9)	8 (13.3)	21 (18.4)
Dizziness	6 (10.9)	5 (8.3)	17 (14.9)
Fatigue	2 (3.6)	3 (5.0)	11 (9.6)

Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide acetate s.c. has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distention, severe epigastric pain, abdominal tenderness and guarding. Occurrence

of gastrointestinal side effects may be reduced by avoiding meals around the time of octreotide acetate s.c. administration, that is, by timing injections between meals or at bedtime.

Octreotide acetate Solution for injection or infusion in the Prevention of Complications Following Pancreatic surgery
Local reactions at the site of injection were the most frequently reported side effects in 247 patients undergoing pancreatic surgery treated with octreotide acetate s.c. for 7 consecutive days starting on the day of the operation, at least 1 hour before laparatomy. Pruritus, exanthema, vomiting, biliary sludge and fever were each reported in 0.4 % of patients and flushes and rash occurred in 0.8% of patients.

Octreotide acetate Solution for injection or infusion in Bleeding Gastro-oesophageal Varices
Raised blood glucose levels were reported in 23 of 98 cirrhotic patients treated with octreotide acetate 25 mcg/hour administered by i.v. infusion over 5 days for the emergency management of bleeding oesophageal varices. Diarrhoea occurred in 5% of patients.

Descriptions of Selected Adverse Reactions

Liver and Biliary
Octreotide acetate and other somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which can lead to gallbladder abnormalities or sludge. Prolonged use of Octreotide Acetate Injection s.c. may result in gallstone formation (see **7 WARNINGS AND PRECAUTIONS**). Pancreatitis may develop in patients on long-term treatment with Octreotide Acetate Injection who develop cholelithiasis.

There have been isolated reports of hepatic dysfunctions associated with octreotide acetate s.c. administration. These consist of the following:

- acute hepatitis without cholestasis and normalization of transaminase values on withdrawal of octreotide acetate s.c. has occurred;
- the slow development of hyperbilirubinemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Endocrine
Because of its inhibitory action on growth hormone, glucagon and insulin, octreotide acetate may impair glucose regulation. Postprandial glucose tolerance may be impaired and in some instances, with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycaemia has also been observed.

Pancreatitis
Acute pancreatitis has been reported in rare instances. Generally, this effect is seen within the first hours or days of octreotide acetate s.c. treatment and resolves on withdrawal of the drug.

Hypersensitivity and anaphylactic reactions
Hypersensitivity reactions have been reported; most hypersensitivity and allergic reactions affect the skin and rarely affect the mouth and airways.

Isolated reports of anaphylactic reaction have been reported. Octreotide acetate administered s.c. and to a much lesser degree by i.v. infusion, can lead to hypersensitivity reaction that may range from generalized pruritus to cardiovascular shock or bronchospasm, with one case of death having been reported.

Cardiac disorder
Cases of bradycardia have been reported (frequency: common). In patients who are predisposed by having relatively low pre-treatment heart rates or whose cardiovascular system is already compromised, as in cirrhotic patients with bleeding oesophageal varices, it is of importance that physicians be alerted to the possible undesirable effect of bradycardia. Tachycardia has also been observed (frequency: uncommon).

Other
Rarely, hair loss has been reported in patients receiving octreotide acetate treatment.

Rarely, dehydration has been reported.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse events (regardless of relationship) occurring at a 1% ≥ incidence <2% reported in the major studies in acromegaly (all doses combined):

Body As a Whole: Oedema peripheral, syncope

Cardiovascular: Hypertension aggravated

Central and Peripheral Nervous Systems: Cramps, vertigo, neuralgia, cramps legs, neuropathy, hyperkinesia

Endocrine: Growth hormone overproduction, hypothyroidism, goiter

Gastro-intestinal System: Gastritis, haemorrhoids, gastroenteritis, haemorrhage rectum, hernia, eructation, gastro-intestinal disorder, stomatitis ulcerative

Hearing and Vestibular: Deafness, ear discharge

Heart Rate and Rhythm: Tachycardia

Liver and Biliary: Hepatitis, liver fatty

Metabolic and Nutritional: Weight increase, hypoglycaemia

Musculo-skeletal System: Arthrosis, surgery, bone fracture, osteonecrosis

Platelet, Bleeding and Clotting: Epistaxis

Psychiatric: Amnesia, sleep disorder

Red Blood Cell: Anaemia hypochromic

Reproductive Disorders: Female: Breast pain female, intermenstrual bleeding, lactation *non purperal*. **Male**: prostate disorder

Resistance Mechanism: Moniliasis, otitis media, pharyngitis, tonsilitis, herpes simplex, herpes zoster

Respiratory System: Dyspnoea, pneumonia

Skin and Appendages: Skin disorder, skin dry, acne, nail disorder

Urinary System: Urinary tract infection, cystitis, dysuria, micturition frequency

Vascular (Extracardiac): Phlebitis, cerebrovascular, vein varicose

Local injection site reactions to Octreotide Acetate Injection may occur and are usually mild and of short duration. These reactions include pain, and rarely swelling and rash.

8.5 Post-Market Adverse Reactions

Spontaneously reported adverse drug reactions are presented below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to octreotide acetate exposure.

Cardiac disorders	Arrhythmias
Blood and lymphatic system disorders	Thrombocytopenia*
Gastrointestinal motility disorder	Ileus, intestinal obstruction
Hepato-biliary disorders	Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice, cholelithiasis, cholecystitis, cholangitis, and pancreatitis, which have sometimes required cholecystectomy
Hypersensitivity	Anaphylaxis, allergy/hypersensitivity reactions
Investigations	Increased alkaline phosphatase levels, increased gamma glutamyl transferase level
Skin and subcutaneous tissue disorders	Urticaria

*Most reports of thrombocytopenia were in patients with liver cirrhosis treated with octreotide acetate (i.v.). This was reversible.

9 DRUG INTERACTIONS

9.2 Drug interactions overview

Many patients with carcinoid syndrome or VIPomas being treated with octreotide acetate s.c. have also been, or are being, treated with many other drugs to control the symptomatology or progression of the disease, generally without serious drug interaction. Included are chemotherapeutic agents, H_2 antagonists, antimotility agents, drugs affecting glycemic states, solutions for electrolyte and fluid support or hyperalimentation, anti-hypertensive diuretics and anti-diarrheal agents.

Where symptoms are severe and octreotide acetate therapy is added to other therapies used to control glycaemic states, such as sulfonylureas, insulin and diazoxide, to beta blockers, calcium channel blockers or to 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 acetate. Adjustment of the dosage of drugs, such as insulin, affecting glucose metabolism may be required following initiation of octreotide acetate therapy in patients with diabetes.

9.4 Drug-Drug Interactions

Since octreotide acetate has been associated with alterations in nutrient absorption, its effect on absorption of any orally administered drugs should be carefully considered. A single case of transplant rejection episode (renal/whole pancreas) in a patient immunosuppressed with cyclosporine has been reported. octreotide acetate treatment to reduce exocrine secretion and close a fistula in this patient resulted in decreases in blood levels of cyclosporine and may have contributed to the rejection episode. octreotide acetate has also been found to delay the intestinal absorption of cyclosporine or cimetidine.

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.
Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by the CYP 3A4 and which have a low therapeutic index should therefore be used with caution (e.g. cyclosporine).

Concomitant use with radioactive somatostatin analogues

Somatostatin and its analogues, such as octreotide, competitively bind to somatostatin receptors and may interfere with the efficacy of radioactive somatostatin analogues.

The administration of Octreotide Acetate Injection should be discontinued 24 hours prior to the administration of lutetium (^{177}Lu) oxodotreotide (LUTATHERA™), a radiopharmaceutical binding to somatostatin receptors.

After administration of lutetium (^{177}Lu) oxodotreotide, Octreotide Acetate Injection may be given for symptomatic management during lutetium (^{177}Lu) oxodotreotide treatment but should be discontinued again 24 hours prior to the next administration of lutetium (^{177}Lu) oxodotreotide.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

In normal healthy subjects, octreotide acetate has been shown to inhibit:

- Release of growth hormone (GH) stimulated by arginine infusion, exercise and insulin- induced hypoglycaemia.
- Postprandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and arginine-stimulated release of insulin and glucagon.
- Thyrotropin releasing hormone (TRH) stimulated release of thyroid stimulating hormone (TSH). The precise mode of action of octreotide acetate on portal hypertension is still unclear. It is thought to reduce splanchnic blood flow primarily by inhibiting vasoactive gastro-intestinal hormone secretion and exerting a direct vasomotor effect on splanchnic vessels, thus reducing portal blood flow. Using human sephanous veins, it has been shown that vasoconstriction is mediated by type 2 somatostatin receptors.

10.2 Pharmacodynamics

The pharmacological activities of octreotide acetate in man include inhibition of stimulated GH secretion, stimulated TSH levels, insulin and glucagon release, gut hormone secretion, and decreased portal hypertension. This spectrum of activity resembles that obtained with administration of somatostatin in man.

The actions of somatostatin are mediated by receptors. Five somatostatin receptor subtypes have been identified. Octreotide displays a high affinity for type 2 receptors, a moderate affinity for type 3 and 5 receptors and a very low affinity for type 1 and 4 receptors.

10.3 Pharmacokinetics

Octreotide acetate Solution for injection or infusion
In man, octreotide acetate is rapidly and completely absorbed after s.c. injection. Peak plasma concentrations reached after s.c. administration are about half of those obtained after intravenous (i.v.) administration of the same dose. Plasma protein binding is about 65%. The uptake in red blood cells is negligible. After i.v. administration there are two disposition half-lives, a short one of about 10 minutes and a longer one of about 1.5 hours. After s.c. administration to healthy volunteers, the final disposition half-life is about 1.5 hours, the volume of distribution is 6 L and the total body clearance is about 160 mL/min. The absolute bioavailability of octreotide acetate calculated after s.c. administration was rather variable, with values of about 100% for 100 mcg and about 130% for 50 mcg and 200 mcg. There is no significant accumulation under conditions of repeated s.c. administration.

11 STORAGE, STABILITY AND DISPOSAL

Octreotide acetate Solution for injection or infusion

For prolonged storage, Octreotide Acetate Injection ampoules must be stored at 2 to 8°C.. For day-to-day use, the ampoules may be stored at room temperature for up to 2 weeks; they must be protected from light. The ampoules should be opened just prior to administration and any unused portion discarded.

Keep container in the outer carton in order to protect from light. Do not freeze

Keep in a safe place out of reach and sight of children and pets.

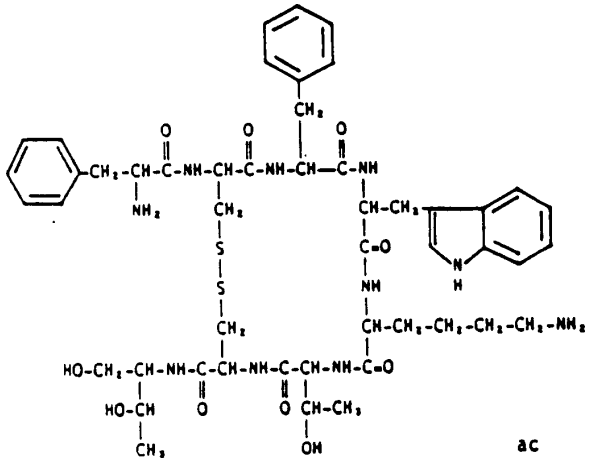
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	octreotide acetate
Chemical name:	D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L threonyl-L-hemicystyl-L-threoninol cyclic(2→7) disulfide acetate
Molecular formula and molecular mass:	$C_{49}H_{66}N_{10}O_{10}S_2$ x (CH_3COOH) x $(H_2O)_y$ 1019.3 g/mol x 60.05 g/mol
Structural formula:	
Physicochemical properties:	Octreotide acetate is a bridged octapeptide analogue of somatostatin. It is a white to off-white amorphous lyophilisate, which melts with decomposition; it is very hygroscopic. The values for pka (I) and pka (II) in water are 7.00 and 10.15 respectively. At 25°C, the solubility of octreotide acetate is >10 mg/mL in water; >10 mg/mL in glacial acetic acid and >10 mg/mL in methanol.

14 CLINICAL TRIALS

As a consequence of market experience, clinical trial data for octreotide acetate injection is not provided.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Single intravenous injections of octreotide acetate were administered to mice and rats. Animals were observed until death occurred or for a period of seven days following administration.

Species	LD_{50}, mg/kg
Mouse	72 (64 - 82)
Rat	18 (15 - 21)

Octreotide acetate caused no unusual effects. Immediately after administration the following signs were observed: numbness, strained and sometimes slower breathing, jumping and roll and stretch cramps. The animals which died did so within one hour, the survivors were without signs after two days.

Subchronic and Chronic Toxicity

Species	Duration	Route	Dose (mg/kg/d)	Observations
Rats	4 weeks	i.p.	1.0, 4.0, 16.0	Low dose: Slightly↓ feed intake, slight ↑ in serum alkaline phosphatase (SAP) values Mid-dose: ↓ weight gain & feed intake, slight ↑ in urine volume & SAP, ↓ serum albumin High Dose: Moderate↓ in weight gain and feed intake, ↓ serum albumin, with slight ↑ in α_2-globulin, slight ↓ in serum glucose, slight ↑ in SGOT and SAP values, unilateral, small, soft testes in 2 M, inhibited spermiogenesis with atrophy of germinal epithelium of seminiferous tubules in 3M. NOAEL: 4 mg/kg/day
Dogs	4 weeks	i.v.	0.2, 0.8, 3.2	Low dose: Sporadic diarrhoea, occasional prolapse of nictitating membrane, hypersalivation Mid dose: Diarrhoea, occasional prolapse of nictitating membrane, howling on injection, hyperemia of the skin of the head. High dose: Frequent diarrhoea, occasional prolapse of nictitating membrane, hypersalivation, hyperaemia of the skin of the head, slight weight loss, slight↑ in urine specific gravity NOAEL: 0.2 mg/kg/day
Rats	26 weeks	i.p.	0.02, 0.1, 1.0	Low dose: No significant findings Mid dose: No significant findings High dose: ↓ feed intake & urine volume ↑ specific gravity of urine in F. NOAEL: 1 mg/kg/day

Species	Duration	Route	Dose (mg/kg/d)	Observations
Dogs	26 weeks + 4 week recovery	i.v.	0.01, 0.05, 0.5	Low dose: Sporadic diarrhoea, sporadic emesis. Scattered single cell necrosis of acidophils, pituitary gland in one F. Mid dose: Frequent diarrhoea, sporadic emesis. Pituitary findings as above in 1 F High dose: Sporadic emesis. Pituitary findings as above in 1 F and 1M All groups: Additional investigation concentrating on determining the nature of the affected pituitary cell showed that octreotide acetate-treated recovery dogs stained positively for prolactin and negatively for growth hormone. Furthermore, plasma levels of prolactin, growth hormone and 17β estradiol were unaffected by octreotide acetate treatment.
Dogs	52 weeks	s.c.	0.24, 0.80, 1.25	Low and mid doses: ↓ lactate dehydrogenase (M) High dose: ↓ lactate dehydrogenase (M & F). 4 M died due to large tissue masses at the injection sites. All available information at present indicates that the findings are species- specific and have no significance to the use of octreotide acetate in humans. All groups: ↓ body weight and body weight gain. Local irritation at the injection site (alopecia, encrustation and thickening/swelling of the skin). ↓ creatinine kinase and aspartate amino transferase. ↑alkaline phosphatases (F) and glucose; ↓ sodium levels; total protein, albumin and α globulin; bilirubin and calcium (F). Urinalysis: ↓ specific gravity and osmolarity; ↑ volume and pH in F only. Microscopically: ↑ incidence of inflammation and hemorrhage of the cutis/subcutis and skin - Abscesses. Sarcomas at the injection sites noted only at 1.25 mg/kg/day. This lesion is considered to be treatment-related. Since the development of sarcomas in sites after repeated injection over long periods of time in rats is a well-known effect, these sarcomas are considered to be expression of a chronic irritant effect of the test article at the high dose level, rather than a direct oncogenic effect.

Species	Duration	Route	Dose (mg/kg/d)	Observations
Dogs	52 weeks	s.c.	0.05, 0.15, 0.30	Low dose: Transient ↓ in food intake in M at start of treatment. Mid dose: Transient ↓ in food intake in M at the start of treatment and ↓ mean body weight gain in M & F; slight but persistent↓ in total protein levels (F at week 52). High dose: Transient ↓ in food intake in M at start of the treatment and ↓ mean body weight gain in M & F; slight but persistent ↓ in total protein levels (F); high incidence of diarrhea in one F (relationship with treatment not clearly established); ↓ in pancreas weight in M (relationship with the treatment unclear). Mid & high doses: ↓ in β phase elimination half-life noted after prolonged administration. Finding may be related to the formation of antibodies to octreotide acetate. No such observations noted in single dose experiments.
Rat	104 weeks	s.c.	0.25, 0.80, 1.25	Control: Microscopically observed sarcomas of the skin/subcutis not as severe as treatment groups Low dose: ↓ body weight gain from week 7 in F. Microscopically observed sarcomas of the skin/subcutis not as severe high dose group. Mid dose: ↓ body weight & body weight gain and ↑relative food consumption in M. Microscopically observed sarcomas of the skin/subcutis not as severe high dose group. High dose: ↓ body weight & body weight gain throughout study and ↑ relative food consumption (more severe in M than F). Microscopically observed sarcomas of the skin/subcutis. All groups (including control): Signs of local irritation at injection site including alopecia, encrustations, scabs and thickening/swelling of skin. Microscopically observed ↑incidence of inflammation, fibrosis, necrosis and hemorrhage associated with s.c. masses.

Additional Toxicity Studies

Species	Duration	Route	Dose (mg/kg/d)	Observations
Dogs	3 weeks	i.v.	0.1 (0.05 b.i.d.)	Treatment: Moderate to severe diarrhoea, ↓ body weight & feed intake. Little variation in basal levels of prolactin or growth hormone. Recovery (staggered recovery periods from 1 to 35 days): Sections of the pituitary revealed development of proliferation foci and heaped nuclei reaching a maximum at 7 days recovery, no longer apparent at day 35 of recovery. Scattered degenerated cells apparent only on days 21 and 35 of recovery.
Monkey (Rhesus)- 6F	3 weeks	i.v.	1.0 (0.5 b.i.d)	Treatment & Recovery periods: No clinical findings attributable to treatment. No diarrhoea, no alterations in basal values of plasma GH, PRL or glucose. Pituitary gland showed no morphological alterations. No treatment related findings in other organs. Electron microscopy revealed no treatment-related alterations in the pituitary.
Dogs	26 weeks	i.v.	0.5	Treatment: Diarrhoea Recovery period (staggered from 6 hours to 12 weeks with 2 animals per period): Focal proliferation and single cell necrosis of pituitary gland. Pituitary function test (dogs treated with an injection of pituitary releasing factor during 1, 8 and 16 weeks of recovery): significant inhibition of stimulated GH release from pituitary up to 8th recovery week; by 14th week, GH response similar to control values.

Carcinogenicity Studies

The results of the oncogenicity studies in rats and mice do not indicate a direct carcinogenic effect of octreotide acetate and are not considered an impediment for human use.

Species	Duration	Route	N/dose	Dose (mg/kg/d)	Observations
Rats (KFM-han Wistar)	116 weeks	s.c.	60M 60F	Placebo, NaCl 0.9%, 0.24, 0.80, 1.25	Mid & high dose: Marginal but statistically significant ↑ in the relative proportion of lymphocytes by 10 to 8% on average in M of mid & high dose groups, and by 16% on average in F of high group, when compared with the controls. Dose-related ↓ in body weight gain in F All groups: No treatment-related differences in inter-current mortality and food intake. Except for the ↑ incidence of injection site nodule (high dose M in particular) and reproductive tract masses/nodules (high dose F), the macroscopic lesions findings did not distinguish treated from control rats. Fast-growing masses at injection sites, particularly in neck region of M. At 1.25 mg/kg/day and 0.24 mg/kg/day, these masses were recorded earlier and at a higher frequency than in other groups of M. They were identified as subcutaneous sarcomata. Alopecia, crusts, sore spots and (scabbed) wounds at the injection sites of both sexes with a higher incidence in the mid & high dose groups. Dose related ↑ in incidence of ovarian sections without corpora lutea. Within the uterus: dose related ↑ in glandular dilatation and ↑ incidence of luminal dilatation (particularly high dose group) when compared to controls. Endometritis observed in all of the treated groups (particularly high dose), but not the controls.
Mice (KFM-han NMRI)	85/86 weeks (F) 98/99 weeks (M)	s.c.	60M 60F	Placebo, NaCl 0.9%, 0.1, 0.4, 1.2, 2.0	0.4, 1.2 & 2 mg/kg/d: ↑ incidence of duodenal mucosal hyperplasia (F) frequently associated with inflammation and duodenal dilatation. All treated-groups: No effect in inter-current mortality, on clinical signs or nodules and masses, food consumption and body weight development. No change in differential blood count. No treatment related change in macroscopical findings. Non neoplastic lesions

Species	Duration	Route	N/dose	Dose (mg/kg/d)	Observations
					at the injection sites identical to those observed in control groups. Neoplastic lesions at the injection sites identical to these observed in control groups.

Genotoxicity

In vitro mutagenicity was tested in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 in the presence and absence of a rat liver S9 homogenate (Ames test). No mutagenic effect was found.

In vivo mutagenicity was investigated by means of the micronucleus test using adult CD mice (Charles River). Octreotide acetate was administered intravenously twice within 24 hours. Doses were 5, 16 or 50 mg/kg for each treatment. Controls received the diluent only. Micronuclei were evaluated in bone marrow preparations made 48 or 72 hours after the first administration. Octreotide acetate was not mutagenic in this test system.

In a second in vivo mutagenicity test, damage to germ cell DNA was evaluated using the unscheduled DNA systhesis (UDS) technique. Male CD mice were injected intravenously with single doses of either 25 or 50 mg/kg. One hour after the administration of octreotide acetate, the mice received an intra-testicular injection of radioactive marked thymidine. Sperm were taken from the cauda epididymis at various time intervals, counted, and tested for radioactivity in a scintillation counter. In this test system octreotide acetate had no effect on the DNA of germ cells.

Reproductive and Developmental Toxicology

Rats and rabbits were treated intravenously with octreotide acetate 0.01, 0.1 or 1 mg/kg/day from day 6 to 15 or 6 to 18 post coitum. Dams and their foetuses were sacrificed at term and examined. In rats and rabbits the 0.01 mg/kg/day dose was well tolerated by the dams but the mid and high doses caused slight dose-dependent weight gain inhibition. No adverse effect on the reproduction data or foetal and placental weight was observed. Morphological findings in foetuses of both species gave no indication of a teratogenic potential of the drug.

In a peri- and post-natal study in rats treated subcutaneously with doses of 0.02, 0.1 or 1.0 mg/kg/day from day 15 post coitum until autopsy on day 21 post-partum, octreotide acetate was well tolerated by the F0 females of all treatment groups, although slightly lower weight gain during pregnancy was noted in the high dose group. The reduced growth observed in rat pups was most likely a direct consequence of the drug's main pharmacological action, i.e. growth hormone inhibition.

In a fertility and general reproduction performance study in female rats treated subcutaneously, once daily, with doses of 0.02, 0.1 or 1 mg/kg/day, octreotide acetate was well tolerated by the F0 dams of the lower and mid dose group. In the high dose group, body weight gain was slightly reduced during the 2 weeks preceding mating and there was localized hair loss at the site of injection. Reproduction performance was normal at all dose levels. Prenatal and post-natal development of F1 offspring was not affected except for some growth retardation. The reproduction performance of F1 animals as well as the development of the F2 offspring were also normal.

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

SUPPORTING PRODUCT MONOGRAPHS

1. SANDOSTATIN and SANDOSTATIN LAR 50 mcg/mL, 100 mcg/mL, 200 mcg/mL, Submission Control Number: 247160, Product Monograph, Novartis Pharmaceuticals Canada Inc. (Apr 19, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Octreotide Acetate Injection

Read this carefully before you start taking **[Pr]Octreotide Acetate Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your health professional about your medical condition and treatment and ask if there is any new information about **[Pr]Octreotide Acetate Injection**.

What is Octreotide Acetate Injection used for?
Octreotide Acetate Injection (octreotide acetate) is used in adults:

- to control symptoms in patients with:
    - metastatic carcinoid tumours. Octreotide Acetate Injection prevents severe diarrhoea and flushing caused by metastatic carcinoid tumours.
    - vasoactive intestinal peptide-secreting tumours (VIPomas). Octreotide Acetate Injection treats excessive watery diarrhoea caused by these tumours.
    - acromegaly. Acromegaly is a condition where there is an overproduction of growth hormones by a gland in the brain.
- to prevent problems following pancreatic surgery
- for the emergency treatment of bleeding in the oesophagus and stomach in patients with liver disease. Octreotide Acetate Injection, used with other interventions, provides better control of bleeding and early re-bleeding.

How does Octreotide Acetate Injection (octreotide acetate) work?

Octreotide Acetate Injection is believed to reduce symptoms by:
- reducing the overproduction of growth hormones made by the pituitary gland (a pea-sized gland located at the base of the brain). Too much growth hormone leads to an increase in the growth of tumours.
- slowing down the overproduction of some specific hormones and other related substances made by the stomach, bowels, or pancreas. This overproduction in hormones can cause flushing and diarrhoea.
- increasing water absorption in the body.

What are the ingredients in Octreotide Acetate Injection?

Medicinal ingredient: octreotide as octreotide acetate

Non-medicinal ingredients: lactic acid, mannitol, sodium bicarbonate and water for injection.

Octreotide Acetate Injection comes in the following dosage form:

- Solution for injection (1 mL ampoules): 50 mcg / mL, 100 mcg / mL or 500 mcg / mL of octreotide as acetate.

Do not use Octreotide Acetate Injection if you:

- are allergic to the octreotide acetate or to any other ingredients of the Octreotide Acetate Injection.

To help avoid side effects and ensure proper use, talk to your health professional before you take Octreotide Acetate Injection. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure (*hypertension*)
- have problems with your blood sugar levels, either too high (*hyperglycaemia*) or too low (*hypoglycaemia*). Taking Octreotide Acetate Injection can also result in diabetes. Your doctor will monitor your blood sugar levels at the beginning of your treatment or when your dosage is changed.
- have or had gallstones or other biliary problems. Long-term use of Octreotide Acetate Injection may result in gallstones or other related problems.
- have or had pancreas problems
- have problems with your liver (e.g. liver cirrhosis)
- have problems with your kidneys and require dialysis
- have heart problems. Abnormal heart rate and rhythm have been reported during treatment with Octreotide Acetate Injection. If you are taking any blood pressure medications, your doctor may adjust your dosage while on Octreotide Acetate Injection.

Other warnings you should know about:
If you take Octreotide Acetate Injection, you may experience the following:

- Growth of tumours. This can cause serious complications (i.e. vision problems). Your doctor will monitor your condition and may provide other treatments.
- Hypothyroidism (low thyroid hormone). If you receive long treatment with Octreotide Acetate Injection your doctor may wish to check your thyroid function periodically.

Pregnancy and breastfeeding

If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.

- Tell your doctor right away if you become pregnant or think you may be pregnant during treatment with Octreotide Acetate Injection.
- Effective birth control methods should be used during treatment with Octreotide Acetate Injection. Talk to your doctor about birth control methods that may be right for you.
- If you are taking Octreotide Acetate Injection to treat acromegaly, there is an increase in risk of you developing the following conditions:
    - Diabetes during pregnancy
    - High blood pressure
    - Worsening of heart disease
- If you are breastfeeding or plan to breastfeed. It is not known if Octreotide Acetate Injection passes into your breast milk. Do not breastfeed during your treatment with Octreotide Acetate Injection.

Nutrition

Taking Octreotide Acetate Injection may alter your ability to absorb vitamin B12 and dietary fat. If you are receiving an intravenous nutritional feeding, zinc levels in your body may also increase. Your doctor will monitor your levels of dietary fat, vitamin B12 and zinc during your treatment.

Tell your health professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Octreotide Acetate Injection:

- drugs to control blood pressure (e.g. beta blockers, calcium channel blockers)
- drugs to control blood sugar (e.g. sulfonylureas, insulin, and diazoxide)
- cimetidine
- cyclosporine
- bromocriptine
- anti-diarrhoeal agents (affect fluid and electrolytes)
- lutetium (^{177}Lu) oxodotreotide (LUTATHERA™), a radiopharmaceutical drug. If you are going to get LUTATHERA treatment, your doctor may stop and/or change your treatment with Octreotide Acetate Injection.

How to take Octreotide Acetate Injection:
Usual dose:

- Your doctor will tell you how much Octreotide Acetate Injection to take each day. The doctor will also tell you how to divide your dosage throughout the day.
- Octreotide Acetate Injection is to be injected under your skin (subcutaneous injection).
- Pay close attention to the amount of drug you are taking into the syringe for injection. Make sure it is the amount your doctor has prescribed for you.

How to Prepare Your Injection of Octreotide Acetate Injection:

You will receive your supply of Octreotide Acetate Injection in ampoules. The ampoules should be visually inspected and not used in the presence of floating particles or discoloration.

Injecting the drug at room temperature, rather than cold from the refrigerator, may lessen the burning sensation that some patients may experience at the injection site.

Ampoules

1. Before breaking open the ampoule, tap the neck portion so that any medication that may be trapped will flow down into the bottom portion of the ampoule.

2. Once the ampoule is opened, insert the needle and pull back the plunger to fill the syringe with the desired amount of drug (your doctor or nurse will tell you how to read the markings on your syringe so that you can fill it with the right amount of drug for your dose). Discard any unused medication.

3. Check to see if there are any air bubbles in the syringe. If bubbles do appear, hold the syringe upright (with the needle pointed up) and lightly tap the barrel. This should make the bubbles rise to the top of the syringe. Then gently press the plunger to push the bubbles out.

How to Inject Your Dose of Octreotide Acetate Injection:

1. Choose the area of your hip, thigh, or abdomen where you want to make your injection.

2. Clean the site with a fresh alcohol wipe, and keep it nearby.

3. Hold the syringe like a pencil, and remove the needle cap.

4. Use the thumb and forefinger of your other hand to gently pinch up a fold of skin at the place you want to inject. This will lift the subcutaneous tissue away from the muscle underneath.

5. Hold the syringe at a 45° angle, and insert the entire length of the needle into the fold of skin in one quick motion.

6. Once the needle is inserted, let go of the skin.

7. Using your free hand, pull back on the plunger slightly to check whether you have placed the needle in a blood vessel (you don't want to). If any blood appears in the syringe, this is not a proper site for your injection. You will have to remove and discard the syringe and needle and start over.

8. Once the needle is inserted properly, slowly inject all of the medication.

9. When you are finished injecting the medicine, place your alcohol wipe where the needle enters the skin. Press lightly.

10. Withdraw the needle at the same angle it is inserted.

11. Gently hold the wipe on your skin for about five seconds.

12. Put the cap back on the needle and dispose of the syringe and needle safely. Do not reuse the syringe and needle. Single-use syringes and needles are used to reduce the chance of infection. Collect your used needles and syringes in a metal container, such as a coffee can, and then dispose of them in a covered garbage can. This will keep others (especially children) from injuring themselves.

Overdose:

If you think you, or a person you are caring for, have injected too much Octreotide Acetate Injection, contact a health professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a scheduled injection, check with your doctor. Do not double your dose at the next injection.

What are possible side effects from using Octreotide Acetate Injection?

These are not all the possible side effects you may have when taking Octreotide Acetate Injection. If you experience any side effects not listed here, tell your health professional.

- arm and leg feel heavy
- arthritis
- behaviour changes
    - anxiety, sadness, moody, bad temper
- congested nose
- constipation
- diarrhoea
- dizziness
- dry mouth
- fainting
- fatty stools, loose stools, discolouration of stools
- feeling of fullness in the stomach
- fever
- flatulence (wind)
- flu and cold-like symptoms
- flushing or hot flashes
- foot, back, joint and leg pain
- headache
- haemorrhoids

- hair loss
- leg cramps
- loss of appetite
- nausea
- nose bleeds
- ringing, buzzing, clicking or hissing in the ears
- sore throat
- stomach pain, stomach discomfort after meal
- swelling, pain, rash, burning sensation or bruising at injection site
- tiredness or inability to sleep
- unusual swelling of the arms, hands, legs, feet and ankles, face
- vomiting
- weakness or lack of energy
- weight gain

Treatment with Octreotide Acetate Injection may cause a change in thyroid function tests and liver function tests.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your health professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Formation of gallstones in the gallbladder (*cholelithiasis*), inflammation of the gallbladder (*cholecystitis*) and inflammation of the bile duct (*cholangitis*): severe pain in the upper right abdomen which may last for several hours, particularly after a fatty meal, possible nausea or vomiting, fever		√	
Vision problems		√	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	
Slow heartbeat (*bradycardia*)		√	
UNCOMMON			
Acute pancreatitis (inflammation of the pancreas gland causing severe stomach pain)			√
Diabetes, worsening diabetes, or high blood sugar unusual thirst, frequent urination, fatigue, blurred vision		√	
Low blood sugar (*hypoglycaemia*): feeling hungry, dizziness, fast heartbeat, tingling, trembling, sweating, feeling tired		√	
Underactive thyroid gland (*hypothyroidism*) causing changes in heart rate, appetite or weight; tiredness, feeling cold, or swelling at the front of the neck.		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your health professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver inflammation (*hepatitis*); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine		√	
Fast heartbeat (*tachycardia*)		√	
RARE			
Allergic skin reactions: rash, hives, itching, redness	√		
UNKNOWN			
Low level of platelet in blood (thrombocytopenia; increased bleeding or bruising, fatigue, weakness		√	
Allergic reaction (*anaphylaxis*) (difficulty in swallowing or breathing, rash, hives, swelling of the face, lips, tongue or throat, tingling, possibly with a drop in blood pressure with dizziness or loss of consciousness)			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your health professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting
- (**https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**) for information on how to report online, by mail or by fax: or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Octreotide Acetate Injection must be stored at 2 to 8°C (in a refrigerator). However, you may leave your daily dose of Octreotide Acetate Injection out at a room temperature of up to 30°C for up to 2 weeks. The ampoules should be opened just prior to administration and any unused portion **discarded**.

Keep the container in the outer carton in order to protect from light. Do not freeze.

Do not use Octreotide Acetate Injection after the expiry date.

Keep out of reach and sight of children and pets.

If you want more information about Octreotide Acetate Injection:

- Talk to your health professional

- Find the full product monograph that is prepared for health professionals and includes this Patient

Medication Information by visiting the Health Canada website: (**https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html**; the manufacturer's website: **www.gmprx.com**, or by calling Generic Medical Partners Inc. at: 416-444-4467

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