PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrOCTREOTIDE for INJECTABLE SUSPENSION

Octreotide for Injectable Suspension

Powder 10 mg, 20 mg, 30 mg octreotide (as acetate) per vial

Intramuscular injection

Synthetic octapeptide analogue of somatostatin (H01CB02)

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RECENT MAJOR LABEL CHANGES

7 WARNING AND PRECAUTIONS, Hepatic/Biliary/Pancreatic	08/2021

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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

Acromegaly

OCTREOTIDE for INJECTABLE SUSPENSION (octreotide acetate) is indicated for acromegalic patients who are adequately controlled with octreotide acetate injection administered subcutaneously, including those in whom surgery, radiotherapy or dopamine agonist treatment is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see 4 DOSAGE AND ADMINISTRATION).

In most patients, octreotide acetate for injectable suspension markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue, osteoarthralagia and carpal tunnel syndrome.

Carcinoid Tumours

OCTREOTIDE for INJECTABLE SUSPENSION is indicated for the treatment of the severe diarrhea and flushing episodes associated with carcinoid tumours in patients in whom symptoms are adequately controlled on subcutaneous treatment with octreotide acetate injection.

Vasoactive Intestinal Peptide Tumours (VIPomas)

OCTREOTIDE for INJECTABLE SUSPENSION is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumours in patients in whom symptoms are adequately controlled on subcutaneous treatment with octreotide acetate injection.

In patients with carcinoid syndrome and VIPomas, the effect of octreotide acetate for injectable suspension on tumour size and rate of growth has not been determined. In patients with carcinoid syndrome and VIPomas, the effect of octreotide acetate for injectable suspension on development of metastases has not been determined.

1.1 Pediatrics

Pediatrics (between birth and 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.4.3 Pediatrics).

1.2 Geriatrics

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

2 CONTRAINDICATIONS

OCTREOTIDE for INJECTABLE SUSPENSION (as 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 for INJECTABLE SUSPENSION may only be administered by deep intragluteal injection. The site of repeat intragluteal injection should be alternated between the left and right gluteal muscle.

OCTREOTIDE for INJECTABLE SUSPENSION should only be administered by a trained healthcare professional. **Do not directly inject diluent without preparing the suspension.** It is important to closely follow the mixing instructions included in the packaging.

OCTREOTIDE for INJECTABLE SUSPENSION must be administered immediately after mixing. OCTREOTIDE for INJECTABLE SUSPENSION should be administered intragluteally at 4-week intervals. Administration of OCTREOTIDE for INJECTABLE SUSPENSION at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled. Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area. **OCTREOTIDE for INJECTABLE SUSPENSION should never be administered by the intravenous or subcutaneous routes.** The following dosage regimens are recommended.

- **Acromegaly**

For patients who are adequately controlled with octreotide acetate injection s.c., it is recommended to start treatment with the administration of 20 mg OCTREOTIDE for INJECTABLE SUSPENSION at 4-week intervals for 3 months. Treatment with OCTREOTIDE for INJECTABLE SUSPENSION can be started the day after the last dose of s.c. octreotide acetate injection. Subsequent dosage adjustments should be based upon serum growth hormone (GH) and insulin-like growth factor 1/somatomedin C (IGF 1) concentrations and clinical symptoms.

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

For patients whose serum GH concentrations are consistently below 1 mcg/L, whose IGF 1 serum concentrations normalized, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg OCTREOTIDE for INJECTABLE SUSPENSION may be administered every 4 weeks. However, particularly in this group of patients, it is recommended to closely monitor adequate control of serum GH and IGF 1 concentrations and clinical signs/symptoms at this low dose of OCTREOTIDE for INJECTABLE SUSPENSION.

For patients in whom surgery, radiotherapy or dopamine agonist treatment is inappropriate, or in the interim period until radiotherapy becomes fully effective, a short test dosing of octreotide

acetate injection s.c. is recommended to assess the response and systemic tolerability of octreotide prior to initiating treatment with OCTREOTIDE for INJECTABLE SUSPENSION as described above.

- **Carcinoid tumours and VIPomas**

Patients not currently treated with octreotide acetate injection s.c. should begin therapy with octreotide acetate injection s.c. The suggested daily dose during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dose is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dose for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.

Octreotide acetate injection s.c. should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide acetate and who tolerate the drug may be switched to OCTREOTIDE for INJECTABLE SUSPENSION in the dosage regimen described below.

Patients currently receiving octreotide acetate injection s.c. can be switched to OCTREOTIDE for INJECTABLE SUSPENSION in a dosage of 20 mg intragluteally at 4-week intervals for 2 months. Gluteal injection sites should be alternated to avoid irritation. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of OCTREOTIDE for INJECTABLE SUSPENSION, carcinoid tumour and VIPoma patients should continue to receive octreotide acetate injection s.c. for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue s.c. injections for this period may result in exacerbation of symptoms. Some patients may require 3 or 4 weeks of such therapy.

After 2 months of a 20 mg dosage of OCTREOTIDE for INJECTABLE SUSPENSION, dosage may be increased to 30 mg every 4 weeks if symptoms are not adequately controlled. Patients who achieve good control on a 20 mg dose may have their dose lowered to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. A dose of 10 mg is not recommended as a starting dose, however, because therapeutically effective levels of octreotide are reached more rapidly with a 20 mg dose.

Dosages higher than 30 mg are not recommended because there is no information on their usefulness.

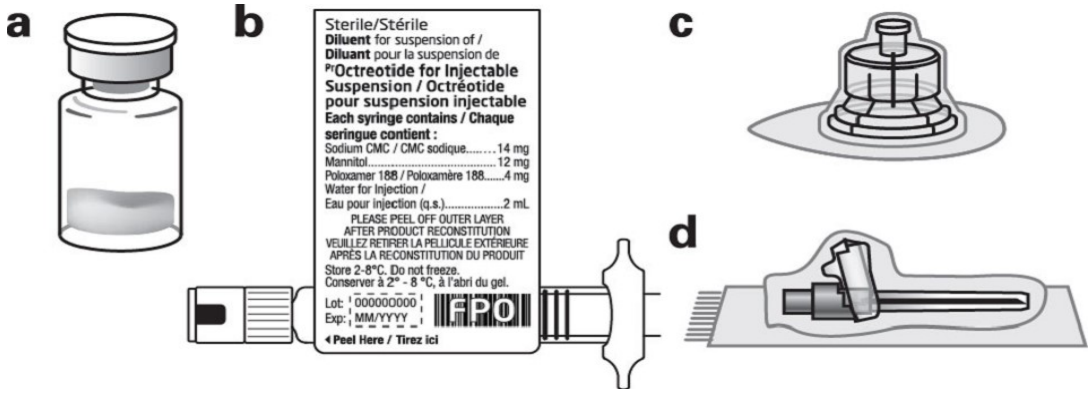
Despite good overall control of symptoms, patients with carcinoid tumours and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on octreotide acetate injection s.c. or octreotide acetate for injectable suspension). During these periods they may be given octreotide acetate injection s.c. for a few days at the dosage they were receiving prior to switching to OCTREOTIDE for INJECTABLE SUSPENSION. When symptoms are again controlled, octreotide acetate injection s.c. can be discontinued.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Preparation of OCTREOTIDE for INJECTABLE SUSPENSION:

OCTREOTIDE for INJECTABLE SUSPENSION is supplied in kits containing:



a. One vial of OCTREOTIDE for INJECTABLE SUSPENSION 10 mg, 20 mg or 30 mg octreotide (as acetate) for injectable suspension

b. One prefilled syringe containing the diluent (showing the peel-off outer syringe label)

c. One vial adapter for drug product reconstitution

d. One 19G x 1.5”safety injection needle

e. The package insert with administration instructions.

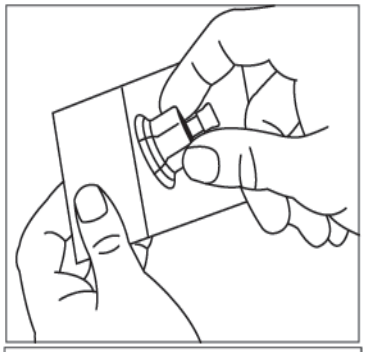
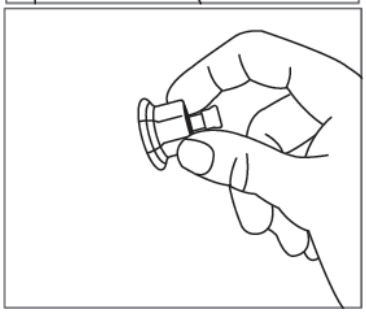
Follow the instructions below carefully to ensure proper reconstitution of OCTREOTIDE for INJECTABLE SUSPENSION before deep intragluteal injection.

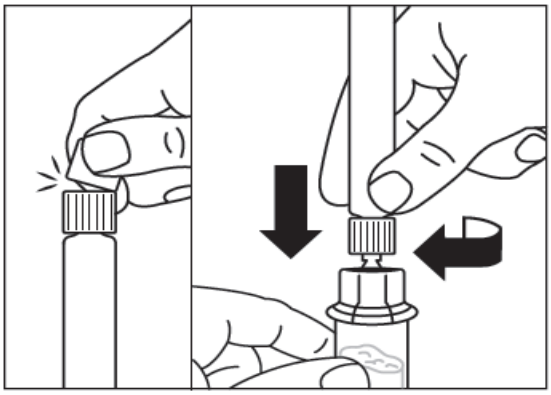
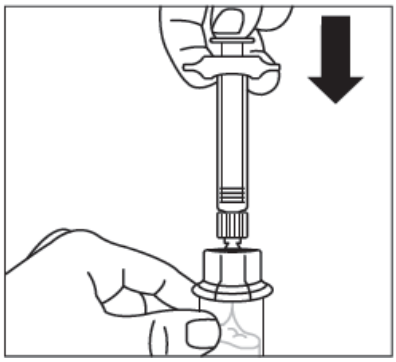
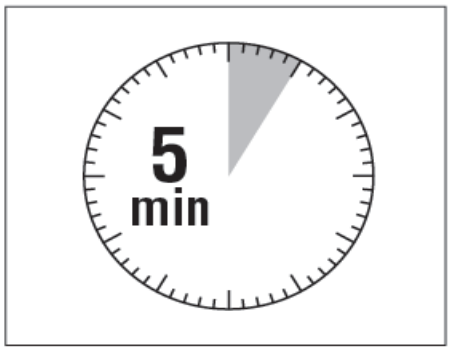
There are 3 critical steps in the reconstitution of OCTREOTIDE for INJECTABLE SUSPENSION. **Not following them could result in failure to deliver the drug appropriately.**

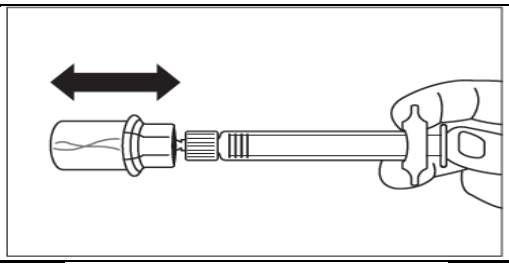
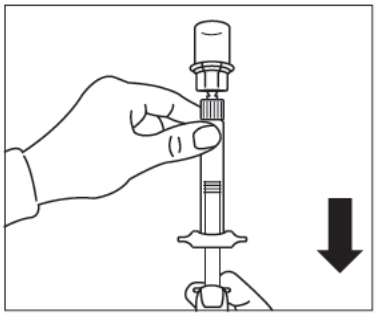
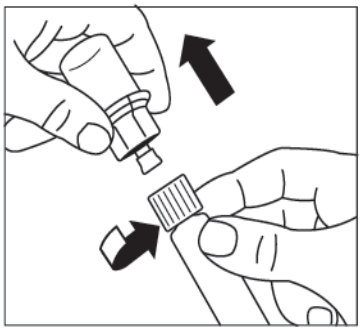
- **The kit must reach room temperature**. Remove the kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- **After adding the diluent, ensure that the powder is fully saturated** by letting the vial stand for 5 minutes.
- After saturation, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until a uniform suspension is formed.** The OCTREOTIDE for INJECTABLE SUSPENSION must only be prepared **immediately** before administration. As with all parenteral admixtures, the constituted product should be examined for the presence of foreign particulate matter, agglomeration or

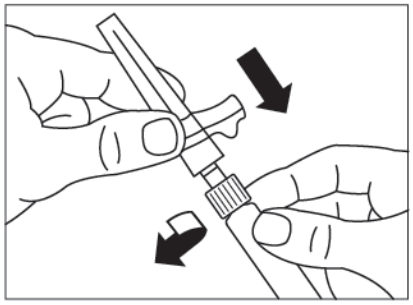
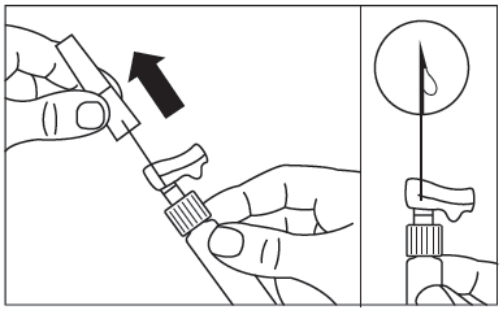
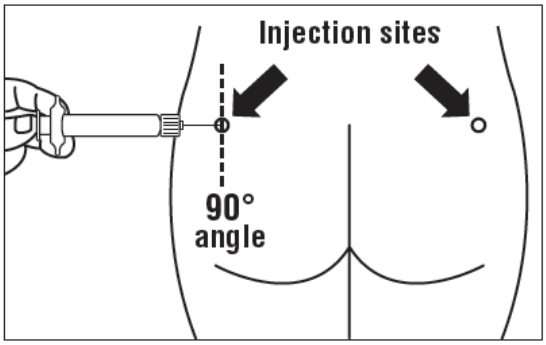
discolouration. Any defective units should be discarded.

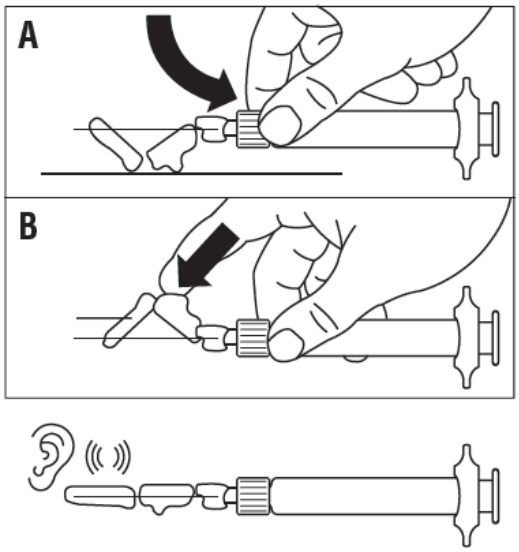
OCTREOTIDE for INJECTABLE SUSPENSION should only be administered by a trained health care professional.

	**Step 1** Remove the OCTREOTIDE for INJECTABLE SUSPENSION kit from refrigerated storage. **ATTENTION: It is essential to start the reconstitution process only after the kit reaches room temperature. Let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.** **Note:** The injection kit can be re-refrigerated if needed.
  	**Step 2** Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol wipe. Peel the blister film and remove the vial adapter from its packaging, by holding between the white luer cap and the skirt. **DO NOT** touch the tip of the access device at any place.

	Place the vial on a flat surface. Position the vial adapter on top of the vial and push it fully down so that it snaps in place, confirmed by an audible “click“. Clean the tip of the vial adapter with an alcohol wipe.
	**Step 3** Snap off the smooth white cap from the syringe prefilled with diluent solution and screw the syringe onto the vial adapter.
	Slowly push the plunger all the way down to transfer all the diluent into the vial.
	**Step 4** **ATTENTION: It is essential to let the vial stand for 5 minutes** to ensure that the diluent has fully saturated the powder. **Note:** It is normal if the plunger rod moves up as there might be a slight overpressure in the vial. **At this stage prepare the patient for injection.**
	Step 5 After the saturation period, make sure that the plunger is pushed all the way down in the syringe. **ATTENTION**: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction **for a minimum of 30 seconds** so

	that the powder is completely suspended (uniform milky suspension). **Repeat moderate shaking for another 30 seconds if the powder is not completely suspended.**
 	**Step 6** Turn syringe and vial upside down, slowly pull the plunger back and draw the entire contents from the vial into the syringe. Unscrew the syringe from the vial adapter.
	**Step 7** The product in the syringe now consists of reconstituted OCTREOTIDE for INJECTABLE SUSPENSION. To avoid confusion, peel off the outer syringe label which corresponds only with the diluent. It is no longer a correct representation of the current contents of the syringe.

 	**Step 8** Prepare the injection site with an alcohol wipe. Screw the safety injection needle onto the syringe. Gently **re-shake** the syringe to ensure a milky uniform suspension. Pull the protective cover straight off the needle Gently tap the syringe to remove any visible bubbles and expel them from the syringe. Proceed **immediately** to Step 9 for administration to the patient. **Any delay may result in sedimentation.**
	**Step 9** OCTREOTIDE for INJECTABLE SUSPENSION must be given only by deep intragluteal injection, **NEVER** intravenously. Insert the needle fully into the left or right gluteus at a 90° angle to the skin. Slowly pull back the plunger to check that no blood vessel has been penetrated (reposition if a blood vessel has been penetrated). Depress the plunger with **steady pressure** until the syringe is empty. Withdraw the needle from the injection site and activate the safety guard (as shown in **Step 10**).

	**Step 10** Activate the safety guard over the needle in one of the 2 methods shown: A. either press the hinged section of the safety guard down onto a hard surface (figure A) B. or push the hinge forward with your finger (figure B) An audible “click” confirms the proper activation. Dispose of syringe immediately (in a sharps container).

OCTREOTIDE for INJECTABLE SUSPENSION must be given only by deep intragluteal injection, never intravenously. If a blood vessel has been penetrated, another injection site must be selected. The site of repeat intragluteal injection should be alternated between the left and right gluteal muscle. Do not use the same gluteal region each time (every 4 weeks).

4.5 Missed Dose

If a scheduled injection is missed, the missed dose should be administered as soon as possible.

5 OVERDOSAGE

A limited number of accidental overdoses of octreotide acetate for injectable suspension have been reported. The doses ranged from 100 mg to 163 mg/month of octreotide acetate for injectable suspension. The only adverse event reported was hot flushes.

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

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

For 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
Intramuscular (intragluteal) injection	10 mg octreotide (free peptide) (11.2 mg octreotide acetate)/vial The powder is white to off-white.	poly (DL-lactide-co-glycolide) 188.8 mg mannitol: 41.0 mg
	20 mg octreotide (free peptide) (22.4 mg octreotide acetate)/vial The powder is white to off-white.	poly (DL-lactide-co-glycolide) 377.6 mg mannitol: 81.9 mg
	30 mg octreotide (free peptide) (33.6 mg octreotide acetate)/vial The powder is white to off-white.	poly (DL-lactide-co-glycolide) 566.4 mg mannitol: 122.9 mg
	Diluent (2 mL) in pre-filled glass syringe The diluent is a clear, colourless solution.	carboxymethylcellulose sodium: 14 mg mannitol: 12 mg poloxamer 188: 4 mg water for injection: q.s. 2 mL

The reconstituted solution is a milky suspension without aggregates.

OCTREOTIDE for INJECTABLE SUSPENSION is supplied in kits containing:

- One single dose 8 mL glass vial of OCTREOTIDE for INJECTABLE SUSPENSION containing 10, 20 or 30 mg of octreotide (as acetate) slow release
- A pre-filled glass syringe containing 2 mL of diluent
- One vial adapter for drug product reconstitution
- One 19G x 1.5” safety injection needle
- The package insert with administration instructions.

7 WARNINGS AND PRECAUTIONS

General

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 for INJECTABLE SUSPENSION 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 hypoglycemia or hyperglycemia. 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 intramuscular injection techniques should be given to the patients and to other persons who may administer OCTREOTIDE for INJECTABLE SUSPENSION (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 injection therapy is occasionally associated with mild transient hypo- or hyperglycemia 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 hypoglycemia. Insulin requirement of patients with type I diabetes mellitus may be reduced by administration of octreotide acetate injection. In non-diabetics and type II diabetics with partially intact insulin reserves, octreotide acetate injection administration can result in prandial increases in glycemia. Severe hyperglycemia, subsequent pneumonia, and death following initiation of octreotide acetate injection therapy was reported in one patient with no history of hyperglycemia.

Predicting the effect of octreotide acetate injection on glucose tolerance in any given patients 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 for INJECTABLE SUSPENSION.

Since following bleeding episodes from esophageal 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 for INJECTABLE SUSPENSION.

- **Thyroid Function**

Data on the effect of chronic therapy with octreotide acetate injection on hypothalamic/pituitary function have not been obtained. A progressive drop in T4 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 injection s.c. daily. Minimal impairment of thyroid function was recorded in some acromegalic patients following treatment with octreotide acetate for injectable suspension. Therefore, baseline and periodic assessment of thyroid function (TSH, total and/or free T4) should be monitored during chronic therapy with octreotide acetate.

Gastrointestinal

- **Nutrition**

There is evidence that octreotide acetate injection therapy may alter absorption of dietary fats in some patients. It is suggested that periodic quantitative 72-hour fecal 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, and monitoring of vitamin B12 levels is recommended during therapy with octreotide acetate for injectable suspension.

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.

In clinical trials 52% of acromegalic patients, most of whom received octreotide acetate for injectable suspension for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge, and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

In clinical trials 62% of malignant carcinoid patients who received octreotide acetate for injectable suspension for up to 18 months developed new biliary abnormalities including gallstones, sludge, and dilatation. New gallstones occurred in a total of 24% of patients.

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 for INJECTABLE SUSPENSION 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 for INJECTABLE SUSPENSION 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 (not

octreotide acetate for injectable suspension). Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of octreotide acetate injection or dosage change. After patients are switched from octreotide acetate injection to octreotide acetate for injectable suspension, GH and IGF-1 determinations may be made after 3 monthly injections of octreotide acetate for injectable suspension. (Steady-state serum levels of octreotide are reached only after a period of 3 months of monthly injections.) Growth hormone can be determined using the mean of 4 assays taken at 1 hour intervals. Somatomedin C can be determined with a single assay. All GH and IGF-1 determinations should be made 4 weeks after the previous octreotide acetate for injectable suspension.

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, therapy should be discontinued.

Patients should undergo a baseline ultrasound examination of the gallbladder and bile ducts prior to commencing octreotide acetate treatment. Periodic ultrasound examination of the gallbladder should be performed, at about 6-month intervals, throughout octreotide acetate treatment. If stones are already present before the start of therapy, the potential benefit of octreotide acetate should be assessed against the potential risks associated with the gallstones. In case of asymptomatic gallstone, octreotide acetate 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 T4 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 injection 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 in the pediatric 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, diarrhea, 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 octreotide acetate injection 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 for injectable suspension in Acromegaly

No clinical studies have been performed which compare octreotide acetate for injectable suspension to placebo. However, the profile of adverse reactions recorded in acromegalic patients treated with octreotide acetate for injectable suspension was similar to that known for octreotide acetate injection s.c. administration. 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. In the double blind studies, gastrointestinal side effects following administration of octreotide acetate for injectable suspension were the most frequent adverse events and included abdominal pain, diarrhea (loose stools), flatulence and steatorrheic stools.

Adverse events occurring in ≥ 2% of patients who participated in the major studies in acromegaly (including their long-term extensions of up to 30 months duration) are listed in the table below, by dose group. It should be noted that some patients may appear under multiple dose levels since some patients switched dose levels.

Table 1 - Adverse Events occurring in ≥ 2 % of patients treated with octreotide acetate for injectable suspension

Adverse Event	Dose Level		
	10 mg n=57 (%)	20 mg n=233 (%)	30 mg n=129 (%)
Application Site			
Injection site pain	1.8	9.0	10.9
Injection site reaction	--	2.1	3.9
Body as a whole			
Influenza-like	8.8	10.3	17.8
symptoms Fatigue	3.5	5.2	11.6
Pain	1.8	5.6	2.3
Surgery	3.5	2.1	6.2
Back pain	1.8	3.4	2.3
Asthenia	3.5	1.3	4.7
Edema	1.8	3.0	1.6
	1.8	1.3	3.9

Table 1 - Adverse Events occurring in ≥ 2 % of patients treated with octreotide acetate for injectable suspension			
Adverse Event	**Dose Level**		
	10 mg n=57 (%)	**20 mg n=233 (%)**	**30 mg n=129 (%)**
Malaise	3.5	1.3	2.3
Accidental trauma	--	2.6	1.6
Hot flushes	--	0.9	3.1
Tumor nos.	--	0.9	3.1
Fever			
Cardiovascular			
Hypertension	1.8	9.9	7
CNS & Peripheral			
Headache	7.0	8.6	12.4
Dizziness	5.3	6.0	10.1
Paresthesia	1.8	3.4	7.0
Cramps	1.8	3.4	3.9
Vertigo	3.5	1.7	1.6
Gastrointestinal			
Diarrhea	7.0	21.5	30.2
Abdominal Pain	12.3	15.0	25.6
Flatulence	12.3	12.4	23.3
Constipation	14.0	8.2	14.7
Nausea	3.5	4.3	7.8
Vomiting	1.8	3.0	6.2
Dyspepsia	1.8	3.0	3.9
Steatorrhea	5.3	1.3	4.7
Feces discoloured	--	2.6	3.9
Tenesmus	--	0.9	3.9
Liver & Biliary			
Cholelithiasis	3.5	7.3	12.4
Gall bladder disorder	--	3.9	7.0
Musculoskeletal			
Arthralgia	--	2.6	6.2
Arthropathy	--	3.0	4.7
Myalgia	1.8	2.1	3.9
Back pain	--	3.0	0.8
Pain leg(s)	3.5	0.9	0.8
Psychiatric Disorder			
Insomnia	3.5	3.9	1.6
Anxiety	--	1.3	4.7
Depression	--	2.1	1.6
Somnolence	1.8	0.4	2.3
Nervousness	--	0.4	2.3
Resistance mechanism	1.8	2.6	3.9
Infection viral	--	2.1	1.6
abscess	1.8	1.7	2.3
Infection			
Respiratory System			
URTI	3.5	3.4	4.7
Coughing	1.8	4.3	3.1
Pharyngitis	1.8	4.3	3.1
Rhinitis	--	--	5.4
Bronchitis	1.8	3.0	1.6
Respiratory disorder	1.8	1.3	3.1

Table 1 - Adverse Events occurring in ≥ 2 % of patients treated with octreotide acetate for injectable suspension			
Adverse Event	**Dose Level**		
	10 mg n=57 (%)	**20 mg n=233 (%)**	**30 mg n=129 (%)**
Sinusitis	1.8	0.9	2.3
Urinary System			
UTI	1.8	2.1	3.1
Cystitis	--	0.9	2.3
Dysuria	--	0.4	2.3
Micturition frequency	--	--	2.3
Skin & Appendages			
Sweating increased	1.8	3.4	4.7
Pruritus	1.8	1.3	4.7
Alopecia	1.8	0.9	3.9
Rash erythematosus	--	2.6	0.8
Rash	3.5	--	--
Other			
Anemia	5.3	6.4	17.1
Conjunctivitis	--	2.1	3.1
Ear disorder	--	--	2.3
Menstrual disorder	--	1.3	2.3
Neoplasm, surgery	--	--	2.3

Descriptions of Selected Adverse Reactions

Liver and Biliary

Octreotide acetate injection 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 may result in gallstone formation (see 7 WARNINGS AND PRECAUTIONS). Pancreatitis may develop in patients on long-term treatment with octreotide acetate who develop cholelithiasis.

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

- acute hepatitis without cholestasis and normalization of transaminase values on withdrawal of octreotide acetate injection 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 hyperglycemia may be induced. Hypoglycemia 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 injection 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 injection 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 esophageal 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: Edema 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, hemorrhoids, gastroenteritis, hemorrhage 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, hypoglycemia

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

Platelet, Bleeding and Clotting: Epistaxis

Psychiatric: Amnesia, sleep disorder

Red Blood Cell: Anemia 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: Dyspnea, 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

Octreotide for Injectable Suspension in Carcinoid Tumours

No clinical studies have been performed which compare octreotide acetate for injectable suspension to placebo. However, the profile of adverse reactions recorded in patients with carcinoid tumours treated with octreotide acetate for injectable suspension was similar to that known for octreotide acetate injection s.c. administration. In a 6-month study during which patients with carcinoid tumours were treated with either octreotide acetate for injectable suspension i.m. at 4-week intervals or octreotide acetate injection s.c. t.i.d., gastrointestinal side effects were the most frequently reported adverse events in both groups and included abdominal pain, diarrhea (loose stools), constipation, flatulence, nausea, and vomiting. The incidences of these adverse events were similar between the 10, 20, and 30 mg dosages of octreotide acetate for injectable suspension.

Local injection site reactions to octreotide acetate 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 injection (i.v.) and some reports were with octreotide acetate for injectable suspension. This was reversible.

9 DRUG INTERACTIONS

9.2 Drug interactions overview

Many patients with carcinoid syndrome or VIPomas being treated with octreotide acetate 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, H2 antagonists, antimotility agents, drugs affecting glycemic states, solutions for electrolyte and fluid support or hyperalimentation, antihypertensive diuretics and anti-diarrheal agents.

Where symptoms are severe and octreotide acetate therapy is added to other therapies used to control glycemic 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 glycemic 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 for INJECTABLE SUSPENSION should be discontinued for at least 4 weeks prior to the administration of lutetium (^{177}Lu) oxodotreotide (LUTATHERA™), a radiopharmaceutical binding to somatostatin receptors. If necessary, patients may be treated with short acting somatostatin analogues until 24 hours prior to the administration of lutetium (^{177}Lu) oxodotreotide.

After administration of lutetium (^{177}Lu) oxodotreotide, treatment with OCTREOTIDE for INJECTABLE SUSPENSION can be resumed within 4 to 24 hours and should be discontinued again 4 weeks 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 hypoglycemia.
- 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 as acetate for injectable suspension
In patients with acromegaly, octreotide acetate for injectable suspension, a galenical formulation of octreotide consisting of microspheres for depot suspension suitable for repeat intramuscular administration at intervals of four weeks, delivers consistent and therapeutic octreotide serum concentrations thus consistently lowering GH and normalizing IGF-1 serum concentrations in the majority of patients.

In patients with carcinoid tumours and Vasoactive Intestinal Peptide Tumours (VIPomas), treatment with octreotide acetate for injectable suspension provides continuous control of symptoms related to the underlying disease.

The pharmacokinetic profile of octreotide acetate after injection of octreotide acetate for injectable suspension reflects the release profile from the polymer matrix and its biodegradation. Once released into the systemic circulation, octreotide distributes according to its known pharmacokinetic properties.

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

In patients with acromegaly, plateau octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg of octreotide acetate for injectable suspension are 358, 926 and 1710 pg/mL,

respectively. Steady state octreotide concentrations reached after three injections at four week intervals, are higher by a factor of approximately 1.6 to 1.8 reaching 1557 and 2384 pg/mL after multiple injections of 20 and 30 mg octreotide acetate for injectable suspension, respectively. No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a period of up to 28 monthly octreotide acetate for injectable suspension injections.

In patients with carcinoid tumours, the mean octreotide serum concentrations after six doses of 10 mg, 20 mg and 30 mg of octreotide acetate for injectable suspension administered by intramuscular injection every four weeks were 1231 pg/mL, 2620 pg/mL and 3928 pg/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 and 30 mg and after three injections of 10 mg.

11 STORAGE, STABILITY AND DISPOSAL

The OCTREOTIDE for INJECTABLE SUSPENSION vials must be stored at 2 to 8 ºC. Keep vial in the outer carton in order to protect it from light. The vials can remain at room temperature on the day of the injection. However the suspension must only be prepared immediately prior to intramuscular (i.m.) injection.

Store the pre-filled syringe with 2 mL diluent at 2 to 8 ºC. Do not freeze.

The OCTREOTIDE for INJECTABLE SUSPENSION powder, once suspended in the diluent, should be used immediately.

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

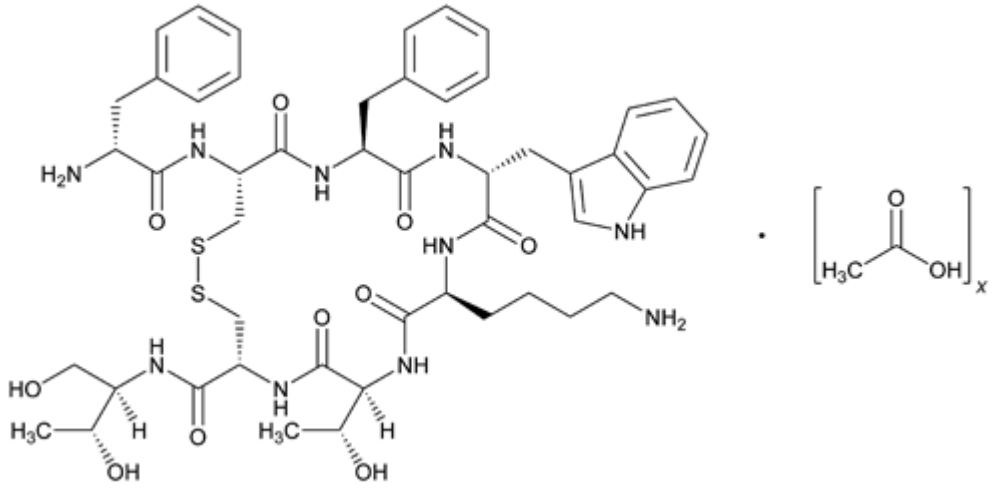
Proper name: octreotide acetate

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: $C_{49}H_{66}N_{10}O_{10}S_2$, $xC_2H_4O_2$

Molecular mass: 1019.2 g/mol (as free base)

Structural formula:



Physicochemical properties: Octreotide acetate is a bridged octapeptide analogue of somatostatin. It is a white to off-white amorphous powder, which melts with decomposition; it is very hygroscopic. Freely soluble in methanol, water and in 1% acetic acid.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The clinical trials of octreotide acetate for injectable suspension were performed in patients who had been receiving subcutaneous octreotide acetate for a period of weeks to as long as 10 years. The acromegaly studies with octreotide acetate for injectable suspension described below were performed in patients who achieved GH levels of <10 ng/mL (and, in most cases <5 ng/mL) while on subcutaneous octreotide acetate injection. However, some patients enrolled were partial responders to subcutaneous octreotide acetate injection, i.e., GH levels were reduced by >50% on subcutaneous octreotide acetate injection compared to the untreated state, although not suppressed to <5 ng/mL.

14.2 Study Results

Acromegaly

Octreotide acetate for injectable suspension was evaluated in three clinical trials in acromegalic patients.

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on octreotide acetate injection given in doses of 100 mcg or 200 mcg t.i.d. Most patients were switched to 20 mg or 30 mg doses of octreotide acetate for injectable suspension given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with octreotide acetate for injectable suspension as they had been on octreotide acetate injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with octreotide acetate injection (most had levels <5 ng/mL). The starting dose of octreotide acetate for injectable suspension was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg or 30 mg every 4 weeks, depending upon the degree of GH suppression. (The recommended regimen for these dosage changes is described under 4 DOSAGE AND ADMINISTRATION.) Growth hormone and IGF-1 were at least as well controlled on octreotide acetate for injectable suspension as they had been on octreotide acetate injection s.c.

Table 2 summarizes the data on hormonal control (GH and IGF-1) for those patients in the first two clinical trials who received all 27 to 28 injections of octreotide acetate for injectable suspension.

Table 2 Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During[1] Treatment with Octreotide acetate for injectable suspension

	Octreotide acetate injection s.c.		Octreotide acetate for injectable suspension	
Mean Hormonal Level	N	%	N	%
GH < 5.0 ng/mL	69/88	78	73/88	83
< 2.5 ng/mL	44/88	50	41/88	47
< 1.0 ng/mL	6/88	7	10/88	11

Table 2 Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During[1] Treatment with Octreotide acetate for injectable suspension				
	Octreotide acetate injection s.c.		Octreotide acetate for injectable suspension	
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
< 2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
< 1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11
[1] Average of monthly levels of GH and IGF-1 over the course of the trials				

For the 88 patients in Table 2, a mean GH level of <2.5 ng/mL was observed in 47% receiving octreotide acetate for injectable suspension. Over the course of the trials 42% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Table 3 summarizes the data on hormonal control (GH and IGF-1) for those patients in the third clinical trial who received all 12 injections of octreotide acetate for injectable suspension.

Table 3 Hormonal Response in Acromegalic Patients Receiving 12 Injections During[1] Treatment with Octreotide acetate for injectable suspension				
	Octreotide acetate injection s.c.		Octreotide acetate for injectable suspension	
Mean Hormonal Level	N	%	N	%
GH < 5.0 ng/mL	116/122	95	118/122	97
< 2.5 ng/mL	84/122	69	80/122	66
< 1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
< 2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
< 1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22
[1] Average of monthly levels of GH and IGF-1 over the course of the trials				

For the 122 patients in Table 3, who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving octreotide acetate for injectable suspension. Over the course of the trial 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to <5 ng/mL on subcutaneous octreotide acetate injection, 95%, compared to 78% across the two previous trials.

In all three trials, GH, IGF-1, and clinical symptoms were similarly controlled on octreotide acetate for injectable suspension as they had been on octreotide acetate injection.

Of the 25 patients who completed the trials and were partial responders to octreotide acetate injection GH >5.0 ng/mL but reduced by >50% relative to untreated levels), 1 patient (4%) responded to octreotide acetate for injectable suspension with a reduction of GH to <2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to <5.0 ng/mL.

Two exploratory open label phase IV studies investigated a 24- and 48-week treatment with octreotide acetate for injectable suspension in previously untreated acromegalic patients. The median reduction in tumour volume was 20.6% in Study B2402 at 24 weeks (n=46) and 29.2% at 48 weeks (n=29), and 24.5% in Study B2401 at 24 weeks (n=91) and 36.2% at 48 weeks (n=84). The percentage change in tumour volume during the course of the investigation was assessed by MRI for the intent-to-treat population. However, the clinical significance has not been established.

Carcinoid Tumours and Vasoactive Intestinal Peptide Tumours (VIPomas)

A 6-month clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to octreotide acetate injection. Sixty-seven patients were randomized at baseline to receive, double-blind, doses of 10 mg, 20 mg or 30 mg octreotide acetate for injectable suspension every 28 days and 26 patients continued, unblinded, on their previous octreotide acetate injection regimen (100-300 mcg t.i.d.).

In any given month after steady-state levels of octreotide were reached, approximately 35%-40% of the patients who received octreotide acetate for injectable suspension required supplemental subcutaneous octreotide acetate injection therapy usually for a few days, to control exacerbation of carcinoid symptoms. In any given month the percentage of patients randomized to subcutaneous octreotide acetate injection, who required supplemental treatment with an increased dose of octreotide acetate injection, was similar to the percentage of patients randomized to octreotide acetate for injectable suspension. Over the six-month treatment period approximately 50%-70% of patients who completed the trial on octreotide acetate for injectable suspension required subcutaneous octreotide acetate injection supplemental therapy to control exacerbation of carcinoid symptoms although steady-state serum octreotide acetate for injectable suspension levels had been reached.

Table 4 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

Table 4 Average No. of Daily Stools and Flushing Episodes (ITT Population)

	Daily Stools (Average No.)			Daily Flushing Episodes (Average No.)	
Treatment	N	Baseline	Last Visit	Baseline	Last Visit
Octreotide acetate injection s.c.	26	3.7	2.6	3.0	0.5
Octreotide acetate for injectable suspension					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

Overall, mean daily stool frequency was as well controlled on octreotide acetate for injectable suspension as on octreotide acetate injection (approximately 2 to 2.5 stools/day).

Mean daily flushing episodes were similar at all doses of octreotide acetate for injectable suspension and on octreotide acetate injection (approximately 0.5 to 1 episode/day).

In a subset of patients with variable severity of disease, median 24 hour urinary 5-HIAA (5-hydroxyindole acetic acid) levels were reduced by 38%-50% in the groups randomized to octreotide acetate for injectable suspension.

The reductions are within the range reported in the published literature for patients treated with octreotide (about 10%-50%).

14.3 Comparative Bioavailability Studies

BIOAVAILABILITY DATA

A randomized, two-treatment, parallel, open label, laboratory-blind, single dose bioequivalence study of OCTREOTIDE for INJECTABLE SUSPENSION 30 mg (Teva Canada Limited) and Sandostatin® LAR®- Monatsdepot 30 mg (Octreotide Acetate for Injectable Suspension) (Novartis Pharma GmbH) following a single intramuscular injection in healthy adults (n=240) under fasting conditions. The results from measured data from 238 subjects who completed the study are summarized in the table below.

Octreotide (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg*hr/ml)	890417.38 934794.94 (33.4)	931186.59 993281.84 (34.6)	95.62	88.49 - 103.33
$AUC_{0\text{-}28days}$ (pg*hr/ml)	504372.55 528095.34 (37.2)	511447.29 558216 (46.6)	98.62	90.72 - 107.20
$AUC_{28\text{-}56days}$ (pg*hr/ml)	351253.21 361270.53 (38.1)	358831.23 379080 (38.6)	97.89	90.36 - 106.04
AUC_I (pg*hr/ml)	942769.62 931877 (39.8)	945348.12 988928 (39.6)	99.73	90.89 - 109.42
C_{max} (pg/ml)	1544.15 1758.35 (67.0)	1557.66 1877.12 (86.4)	99.13	88.91 - 110.53
T_{max}§ (h)	289.50 (0.50-816.52)	288.50 (1.00- 772.42)		
$T_{½}$€ (h)	123.20 (108.9)	130.06 (58.4)		

* Octreotide for Injectable Suspension (octreotide acetate) 30 mg (Teva Canada Limited)
†Sandostatin® LAR®- Monatsdepot 30 mg Injectable Suspension (Novartis Pharma GmbH), Country of purchase: Germany
§ Expressed as median (range)
€ Expressed as the arithmetic mean (CV%)

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 3 M. NOAEL: 4 mg/kg/day
Dogs	4 weeks	i.v.	0.2, 0.8, 3.2	Low dose: Sporadic diarrhea, occasional prolapse of nictitating membrane, hypersalivation Mid dose: Diarrhea, occasional prolapse of nictitating membrane, howling on injection, hyperemia of the skin of the head. High dose: Frequent diarrhea, occasional prolapse of nictitating membrane, hypersalivation, hyperemia 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

Species	Duration	Route	Dose (mg/kg/d)	Observations
				High dose: ↓ feed intake & urine volume ↑ specific gravity of urine in F. NOAEL: 1 mg/kg/day
Dogs	26 weeks + 4 week recovery	i.v.	0.01, 0.05, 0.5	Low dose: Sporadic diarrhea, sporadic emesis. Scattered single cell necrosis of acidophils, pituitary gland in one F. Mid dose: Frequent diarrhea, sporadic emesis. Pituitary findings as above in 1 F High dose: Sporadic emesis. Pituitary findings as above in 1 F and 1 M 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.
Dogs	52 weeks	s.c.	0.05, 0.15, 0.30	Low dose: Transient ↓ in food intake in M at start of treatment.

Species	Duration	Route	Dose (mg/kg/d)	Observations
				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 diarrhea, ↓ 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

Additional Toxicity Studies

Species	Duration	Route	Dose (mg/kg/d)	Observations
				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 diarrhea, 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: Diarrhea 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.

Chronic Toxicity Studies with octreotide acetate for injectable suspension

Species	Duration	Route	N/dose	Dose	Observations
Rat/CR-SD	26 weeks 17 weeks (recovery)	i.m. bilateral injection into biceps femoris muscles	15M/15F 15M (recovery)	0, 2.5 mg in 0.5 mL 0.5% sodium CMC every 4 weeks	All groups (including controls): No deaths and no drug related signs or changes in clinical pathology parameters. Reversible granulomatous myositis at injection sites. Benign hemangiomas at injection site. This is related to the i.m. injection of the Microspheres of octreotide acetate for injectable suspension
Rat/CR-SD	24 weeks 39 weeks (recovery)	i.m.	50M	0, 2.5 mg	2.5 mg group: ↓ body weights compared to controls. This finding was not present at the end of recovery period. All groups: No treatment related

Species	Duration	Route	N/dose	Dose	Observations
					findings. No hyperplastic or neoplastic findings and no hemangiomas at injection sites.

Carcinogenicity

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 intercurrent 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	85/86	**s.c.**	60M	Placebo,	0.4, 1.2 & 2 mg/kg/d: ↑ incidence of

Species	Duration	Route	N/dose	Dose (mg/kg/d)	Observations
(KFM-han NMRI)	weeks (F) 98/99 weeks (M)		60F	NaCl 0.9%, 0.1, 0.4, 1.2, 2.0	duodenal mucosal hyperplasia (F) frequently associated with inflammation and duodenal dilatation. <u>All treated-groups:</u> No effect in intercurrent 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 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.

The octreotide acetate for injectable suspension microspheres were devoid of mutagenic potential when tested in a validated *in vitro* bacterial assay.

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 fetuses 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 fetal and placental weight was observed. Morphological findings in fetuses 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.

Special Toxicology

Special Toxicity Studies with octreotide acetate for injectable suspension: Local Tolerance

Species	Duration	Route	N/dose	Dose	Observations
Rat/CD	Single dose	i.m. bilateral (gastrocnemius muscle)	18M 9M (Control)	0, 20 mg in 0.2 mL 0.5% sodium CMC	Animals sacrificed sequentially at 9 time points between day 2 and day 92. Microencapsulated octreotide acetate well tolerated with no treatment related clinical signs or findings. No difference in response at injection site between diluent control and drug loaded microspheres.
Rat CR/CD	Single dose	i.m. injection (gastrocnemius muscle)	7M	Control (LAR microsphere diluent); 2 mg	One animal per group sacrificed on days 5, 15, 30, 45, 60, 75 and 90. No adverse histologic findings at injection sites and no difference in muscle histopathology or pattern of microcapsule degradation
Rabbit NZW	Single dose	i.m. bilateral (sacrospinalis	9M	0, 25 mg (in 2.0	Animals sacrificed sequentially at 9 time

Species	Duration	Route	N/dose	Dose	Observations
		muscles)		mL 0.5% sodium CMC)	points between day 2 and day 92. Microencapsulated octreotide acetate well tolerated with no treatment-related clinical signs or mortality. No difference in response at injection site between diluent control and drug loaded microspheres.
Rabbit NZW	Single dose	i.m.	7M	Control (LAR microsphere diluent), 25 mg	One animal per group sacrificed on days 5, 15, 30, 45, 60, 75 and 90. No difference in response between diluent control and drug loaded microspheres.

17 SUPPORTING PRODUCT MONOGRAPHS

SANDOSTATIN® LAR® (octreotide acetate for injectable suspension, 10 mg, 20 mg, and 30 mg per vial), Submission Control No. 247160, Product Monograph, Novartis Pharmaceuticals Canada Inc.. Date of Revision: APR 19, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOCTREOTIDE for INJECTABLE SUSPENSION
Octreotide (as acetate) for Injectable Suspension

Read this carefully before you start taking **OCTREOTIDE for INJECTABLE SUSPENSION** 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 **OCTREOTIDE for INJECTABLE SUSPENSION**.

What is OCTREOTIDE for INJECTABLE SUSPENSION used for?

OCTREOTIDE for INJECTABLE SUSPENSION is used in adults who are adequately being treated with octreotide acetate injection for:

- metastatic carcinoid tumours. OCTREOTIDE for INJECTABLE SUSPENSION treats severe diarrhea and flushing caused by metastatic carcinoid tumours
- vasoactive intestinal peptide-secreting tumours (VIPomas). OCTREOTIDE for INJECTABLE SUSPENSION treats excessive watery diarrhea caused by these tumours.
- acromegaly. Acromegaly is a condition where there is an overproduction of growth hormones by a gland in the brain. OCTREOTIDE for INJECTABLE SUSPENSION is used to treat people with acromegaly:
    - when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or haven't worked;
    - to cover the interim period until the radiotherapy becomes fully effective.

How does OCTREOTIDE for INJECTABLE SUSPENSION work?

OCTREOTIDE for INJECTABLE SUSPENSION is believed to provide treatment 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 diarrhea.
- increasing water absorption in the body.

What are the ingredients in OCTREOTIDE for INJECTABLE SUSPENSION?

Medicinal ingredient: octreotide as octreotide acetate.

Non-medicinal ingredients

Powder (in vial): poly (DL-lactide-co-glycolide) and mannitol.

Diluent (in prefilled syringe): carboxymethylcellulose sodium, mannitol, poloxamer 188 and

sterile water.

OCTREOTIDE for INJECTABLE SUSPENSION comes in the following dosage forms:

OCTREOTIDE for INJECTABLE SUSPENSION is supplied in a kit which includes:

- One glass vial
    - Powder for suspension (8 mL glass vial): 10 mg, 20 mg or 30 mg of octreotide (as acetate);
- A pre-filled glass syringe containing 2 mL of diluent to be used for suspending the powder;
- One vial adapter to be used for delivering the diluent from the pre-filled syringe to the vial, without a needle;
- One 19G x 1.5" safety injection needle;
- A package insert for detailed directions for use.

Do not use OCTREOTIDE for INJECTABLE SUSPENSION if you:

- Are allergic to octreotide acetate or any other ingredients in OCTREOTIDE for INJECTABLE SUSPENSION and its package.

To help avoid side effects and ensure proper use, talk to your health professional before you take OCTREOTIDE for INJECTABLE SUSPENSION. 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 (*hyperglycemia*) or too low (*hypoglycemia*). Taking OCTREOTIDE for INJECTABLE SUSPENSION 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 for INJECTABLE SUSPENSION may result in gallstones and 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 for INJECTABLE SUSPENSION. If you are taking any blood pressure medications, your doctor may adjust your dosage while on OCTREOTIDE for INJECTABLE SUSPENSION.

Other warnings you should know about:

If you take OCTREOTIDE for INJECTABLE SUSPENSION, 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-term treatment with OCTREOTIDE for INJECTABLE SUSPENSION 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 for INJECTABLE SUSPENSION
- Effective birth control methods should be used during treatment with OCTREOTIDE for INJECTABLE SUSPENSION. Talk to your doctor about birth control methods that may be right for you.
- If you are taking OCTREOTIDE for INJECTABLE SUSPENSION 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 for INJECTABLE SUSPENSION passes into your breast milk. Do not breastfeed during your treatment with OCTREOTIDE for INJECTABLE SUSPENSION.

Nutrition

Taking OCTREOTIDE for INJECTABLE SUSPENSION 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 for INJECTABLE SUSPENSION:

- 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-diarrheal 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 for INJECTABLE SUSPENSION.

How to take OCTREOTIDE for INJECTABLE SUSPENSION:

- Your doctor or nurse will give you your injection of OCTREOTIDE for INJECTABLE SUSPENSION.
- OCTREOTIDE for INJECTABLE SUSPENSION is injected into the muscles of your buttocks. For each injection, the doctor or nurse should alternate between the left and right

buttocks.

- The vials should be examined before use. Do not use if the vial is damaged, the powder is discoloured, or contains unusual particulate matter.

Usual dose

Dose: One vial every 4 weeks

Usual starting dose: 20 mg every 4 weeks. The dose may be changed later depending on your condition.

Overdose:

If you think you, or a person you are caring for, have been given too much OCTREOTIDE for INJECTABLE SUSPENSION, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your injection, please contact your doctor as soon as possible.

What are possible side effects from using OCTREOTIDE for INJECTABLE SUSPENSION?

These are not all the possible side effects you may have when taking OCTREOTIDE for INJECTABLE SUSPENSION. If you experience any side effects not listed here, tell your health professional.

- behaviour changes
  - anxiety, sadness, moody, nervous, inability to sleep
- breast pain
- cold
  - runny or stuffy nose, sore throat, cough, sinus congestion, body aches, sneezing
- constipation
- cramps
- diarrhea
- discoloration of stools
- dizziness
- fainting
- fatty stools
- feeling of fullness in the stomach
- fever
- flatulence (wind)
- flu-like symptoms
- hair loss
- having the urge to empty your bowels
- headache
- hot flashes
- increased sweating

- indigestion
- joint, leg(s), muscle, or back pain
- loss of appetite
- nausea
- nose bleeds
- pain, swelling and/or rash at injection site
- rash or itchy skin
- stomach discomfort after meal
- stomach pain
- tiredness
- unusual swelling of the arms, hands, legs, feet and ankles, face
- vomiting
- weakness or lack of energy

Treatment with OCTREOTIDE for INJECTABLE SUSPENSION 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 ducts (*cholangitis*) (severe pain in the upper right abdomen which may last for several hours, particularly after a fatty meal, possible nausea or vomiting, fever)		√	
Anaemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		√	
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)			√

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	
Low blood sugar (*hypoglycemia*): feeling hungry, dizziness, fast heartbeat, tingling, trembling, nervousness, sweating, feeling tired		√	
Diabetes, worsening of diabetes, or high blood sugar: unusual thirst, frequent urination, fatigue, blurred vision		√	
Underactive thyroid gland (*hypothyroidism*) causing changes in heart rate, appetite or weight; tiredness, feeling cold, or swelling at the front of the neck.		√	
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 healthcare 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:

The OCTREOTIDE for INJECTABLE SUSPENSION powder and diluent should be stored at 2°C to 8°C (in a refrigerator). Do not freeze. Keep the vial in the outer carton in order to protect it from light. The vials should be allowed to reach room temperature on the day of the injection, but must be protected from light. However, the suspension must only be prepared immediately before injection. Once removed from the refrigerator, the vials will usually reach room temperature within 30 to 60 minutes.

Do not use OCTREOTIDE for INJECTABLE SUSPENSION after the expiry date.

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

If you want more information about OCTREOTIDE for INJECTABLE SUSPENSION:

- Talk to your healthcare 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 http://wwww.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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