PRODUCT MONOGRAPH

Pr OCTREOTIDE ACETATE OMEGA

(Octreotide Acetate Injection)

50 µg/ mL, 100 µg/ mL, 200 µg/ mL, 500 µg/ mL

Sterile

Synthetic Octapeptide Analogue of Somatostatin

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OCTREOTIDE ACETATE OMEGA

(Octreotide Acetate Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous and intravenous infusion	Solution in single-use vial (1 mL): 50µg/mL, 100 µg/mL, 500 µg/mL or Multidose Vial (5 mL): 200 µg/ mL	50, 100, 500 µg/mL Glacial Acetic Acid, Sodium Acetate Trihydrate, Sodium Chloride. 200 µg/mL Glacial Acetic Acid, Sodium Acetate Trihydrate, Sodium Chloride, Phenol. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

OCTREOTIDE ACETATE OMEGA s.c. Single-use and Multidose vials

General

OCTREOTIDE ACETATE OMEGA (octreotide acetate) therapy is indicated for control of symptoms in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumors (VIPomas) as well as in patients with acromegaly.

Data are insufficient to determine whether OCTREOTIDE ACETATE OMEGA decreases the size, rate of growth, or development of metastases in patients with these tumors.

OCTREOTIDE ACETATE OMEGA is also indicated for the prevention of complications following pancreatic surgery in patients undergoing high risk procedures.

OCTREOTIDE ACETATE OMEGA is also indicated for the emergency management of bleeding gastrooesophageal varices in patients with cirrhosis and as protection from rebleeding. OCTREOTIDE ACETATE OMEGA is used in association with specific intervention such as endoscopic sclerotherapy.

Carcinoid Tumors

OCTREOTIDE ACETATE OMEGA is indicated for the symptomatic treatment of metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Vasoactive Intestinal Peptide Tumors (VIPomas)

OCTREOTIDE ACETATE OMEGA is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Significant improvement has been noted in the overall condition of these otherwise therapeutically unresponsive patients. Therapy with OCTREOTIDE ACETATE OMEGA results in improvement in electrolyte abnormalities, e.g., hypokalemia, often enabling reduction of fluid and electrolyte support.

Acromegaly

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

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

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

In most patients, OCTREOTIDE ACETATE OMEGA markedly reduces the clinical symptoms of the disease such as headache, skin and soft tissue swelling, hyperhydrosis, arthralgia, paresthesia. In patients with a large pituitary adenoma, OCTREOTIDE ACETATE OMEGA treatment may result in some shrinkage of the tumour mass.

Prevention of Complications following Pancreatic Surgery

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

Bleeding Gastro-oesophageal Varices

In patients presenting with bleeding gastro-oesophageal varices due to underlying cirrhosis,

OCTREOTIDE ACETATE OMEGA (octreotide acetate) administration in combination with specific intervention (e.g. sclerotherapy) provides better control of bleeding and early rebleeding, reduces transfusion requirements and improves 5-day survival).

CONTRAINDICATIONS

OCTREOTIDE ACETATE OMEGA (octreotide acetate) is contraindicated in patients with a known hypersensitivity to octreotide or to any of the excipients.

WARNINGS AND PRECAUTIONS

General

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

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

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in 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.

Carcinogenesis and Mutagenesis

Studies in laboratory animals have demonstrated no mutagenic potential of octreotide acetate. No long-term studies in animals to assess carcinogenicity have been completed. Octreotide Acetate Injection s.c. did not impair fertility in rats at doses up to 1000 µg/kg/day.

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 (see WARNINGS AND PRECAUTIONS). 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 rechallenge (see 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 OMEGA 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 OMEGA. In non-diabetics and type II diabetics with partially intact insulin reserves, OCTREOTIDE ACETATE OMEGA 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 OMEGA 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 ACETATE OMEGA s.c.

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 ACETATE OMEGA s.c.

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 T_4 levels has been reported, culminating in clinical and biochemical hypothyroidism after 19 months of therapy in one clinical trial patient (carcinoid) receiving 1500 µg of Octreotide Acetate Injection s.c. daily. Minimal impairment of thyroid function was recorded in some acromegalic patient following treatment with Octreotide acetate long-acting release. Therefore, baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) should be monitored during chronic therapy with octreotide acetate.

Gastrointestinal

Nutrition

There is evidence that Octreotide Acetate 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.

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 long-acting release injection 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.

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.

It is recommended that patients on extended therapy with OCTREOTIDE ACETATE OMEGA be evaluated periodically (at about 6 to 12-month intervals) using ultrasound evaluations of the gallbladder and bile ducts.

Baseline and periodic (at about 6 to 12-month intervals) ultrasonography is recommended during therapy with OCTREOTIDE ACETATE OMEGA to assess the presence of gallstones. If gallstones do occur, they are usually asymptomatic. Symptomatic gallstones should receive medical attention.

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

Patient Information

Careful instruction in sterile subcutaneous and intramuscular injection techniques should be given to the patients and to other persons who may administer OCTREOTIDE ACETATE OMEGA Injection (see CONSUMER INFORMATION).

Patients with carcinoid tumors 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.

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.

Sexual Function/Reproduction

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.

Special Populations

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.

Nursing Women: 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 OMEGA treatment.

Pediatrics: Experience with Octreotide Acetate Injection s.c. 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 μg/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 μg subcutaneous dose of Octreotide Acetate Injection.

Monitoring and Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. 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 OMEGA Injection. Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of OCTREOTIDE ACETATE OMEGA Injection or dosage change. 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.

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy (see WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse reactions reported with Octreotide Acetate Injection (octreotide as acetate) include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

OCTREOTIDE ACETATE INJECTION s.c. Single-use and Multidose Vials in GEP and Acromegaly:

Table 1 - Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumor Patients and 114 Acromegalic Patients Treated with OCTREOTIDE ACETATE INJECTION

Adverse Reaction Profile According to Body System	GEP Endocrine Tumor Patients (n=196) %	Acromegalic Patients (n=114) %
Gastrointestinal S.		
Diarrhea	6.6	57.9
Abdominal discomfort	4.1	43.9
Stools Loose	3.1	36.0
Nausea	8.7	29.8
Flatulence	0.5	13.2
Constipation	1.0	8.8
Abdominal distention	-	7.9
Stools abnormal	0.5	6.1
Cholelithiasis	<1.0	4.4
Rectal gas	-	4.4
Vomiting	2.6	4.4
Fatty stools	3.6	-
GI bleeding	0.5	-
Rectal disorders	0.5	-
Hemorrhoids	-	1.8
Cholecystitis	-	1.8
Eructations	-	1.8
Integumentary S.		
Pain at injection site	8.2	9.6
Acne	-	4.4
Bruise	0.5	4.4
Pruritus	-	4.4
Alopecia/Baldness/Hair loss	1.0	3.5
Musculoskeletal S.		
Backache/pain	0.5	4.4
Joint pain	-	4.4
Arthritis	-	2.6
Arm/leg heavy - tired	-	2.6
Leg ache/pain	-	2.6

Table 1 - Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumor Patients and 114 Acromegalic Patients Treated with OCTREOTIDE ACETATE INJECTION

Adverse Reaction Profile According to Body System	GEP Endocrine Tumor Patients (n=196) %	Acromegalic Patients (n=114) %
Osteoarthritis	-	1.8
Vertebral disk disorder	-	1.8
Twitching	-	1.8
Respiratory S.		
Throat pain	0.5	2.6
Flu symptoms	-	6.1
Cold symptoms	-	6.1
Sinusitis	-	3.5
Nasal congestion	-	1.8
Cardiovascular S.		
Leg cramps	-	3.5
Dyspnea	-	1.8
Epistaxis	-	1.8
Chest pain	0.5	-
Edema	1.0	2.6
Ischemic Attack	0.5	-
Hypertension	0.5	-
Thrombophlebitis	0.5	-
Cramps	-	2.6
Autonomic S.		
Visual disturbances	0.5	2.6
Mouth dry/furry/xerostomia	0.5	1.8
Flushing	0.5	1.8
Numbness	-	1.8
Hot flash	-	1.8
Central Nervous S.		
Headache	1.5	18.4
Dizziness	1.5	14.9
Fatigue	1.0	9.6
Anxiety/Nervousness	0.5	2.6
Asthenia	0.5	-
Bell's palsy	0.5	-
Seizure	0.5	-
Depression	0.5	2.6
Sleepiness/insomnia	0.5	1.8
Weakness	1.0	-
Moody	-	2.6
Appetite loss	-	1.8
Irritability	-	1.8
Tinnitus	-	1.8
Urogenital S.		
Urinary tract infection	-	6.1
Pollakiuria	-	3.5
Vagina infection	-	2.6
Vagina itch	-	1.8
Breast lump	-	1.8
Dysuria	-	1.8
Kidneys, pain in	-	1.8
Polyuria	-	1.8

Table 1 - Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumor Patients and 114 Acromegalic Patients Treated with OCTREOTIDE ACETATE INJECTION

Adverse Reaction Profile According to Body System	GEP Endocrine Tumor Patients (n=196) %	Acromegalic Patients (n=114) %
Prostatitis	-	1.8
Tumor breast	-	1.8
Hematologic		
Hematoma, injection site	-	9.6
Endocrine S.		
Hypoadrenalism	-	2.6
Hypothyroidism	-	1.8
Hypogonadism	-	1.8
Hypoglycemia	-	1.8
Miscellaneous		
Foot pain	-	1.8
Fever	-	1.8
Otitis	-	1.8
Weight gain	-	1.8

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

In clinical trials, acromegalic patients had a higher incidence of diarrhea, abdominal pain/discomfort, nausea and loose stools than patients treated with Octreotide Acetate Injection s.c. for other indications. It is believed that the primary reason for this observation is that patients who received Octreotide Acetate Injection s.c. for carcinoid syndrome, VIPoma and other gastroenteropancreatic tumors had these gastrointestinal symptoms at baseline and would only report them as adverse events if they became more frequent or severe during OCTREOTIDE ACETATE OMEGA s.c. treatment.

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

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

Specific Adverse Event by Body System	Placebo B301 (n=55)%	Octreotide Acetate Injection B301 (n=60)%	Octreotide Acetate Injection B301, B302 & B303 (n=114)%
Skin			
Pain at injection site	2 (3.6)	5 (8.3)	11 (9.6)
Acne	--	2 (3.3)	5 (4.4)
Bruise	1 (1.1)	2 (3.3)	5 (4.4)
Pruritus	--	--	5 (4.4)

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

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

Gastrointestinal side effects include anorexia, nausea, vomiting, crampy abdominal pain, abdominal bloating, flatulence, loose stools, diarrhea and steatorrhea. Although measured fecal fat excretion may increase, there is no evidence to date that long-term treatment with Octreotide Acetate Injection s.c. has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distention, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of Octreotide Acetate Injection s.c. administration, that is, by timing injections between meals or at bedtime.

Octreotide Acetate Injection s.c. Single-Use and Multidose Vials in the Prevention of Complications Following Pancreatic surgery

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

Octreotide Acetate Injection Single-Use and Multidose Vials in Bleeding Gastro-oesophageal Varices

Raised blood glucose levels were reported in 23 of 98 cirrhotic patients treated with Octreotide Acetate Injection 25 µg/hour administered by i.v. infusion over 5 days for the emergency management of bleeding oesophageal varices. Diarrhea occurred in 5% of patients.

In a 6-month study during which patients with carcinoid tumors were treated with Octreotide Acetate Injection s.c. t.i.d., gastrointestinal side effects were the most frequently reported adverse events including abdominal pain, diarrhea (loose stools), constipation, flatulence nausea and vomiting.

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

General:

Prolonged use of OCTREOTIDE ACETATE OMEGA s.c. may result in gallstone formation (see WARNINGS AND PRECAUTIONS). Pancreatitis may develop in patients on long-term treatment with OCTREOTIDE ACETATE OMEGA who develop cholelithiasis.

Because of its inhibitory action on growth hormone, glucagon and insulin, OCTREOTIDE ACETATE OMEGA s.c. 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.

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.

Rarely, hair loss has been reported in patients receiving Octreotide Acetate Injection s.c. treatment.

Rarely, hypersensitivity reactions have been reported.

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.

Isolated reports of bradycardia have been reported. 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.

There have been isolated reports of hepatic dysfunctions associated with Octreotide Acetate Injection s.c. 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.

Rarely, dehydration has been reported.

Post-Market Adverse Drug 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 Injection exposure.

Cardiac disorders	Arrhythmias
Hepato-biliary disorders	Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice
Hypersensitivity	Anaphylaxis, allergy/hypersensitivity reactions
Investigations	Increased alkaline phosphatase levels, increased gamma glutamyl transferase level
Skin and subcutaneous tissue disorders	Urticaria.
Gastrointestinal motility disorder	Ileus, intestinal obstruction

DRUG INTERACTIONS

Drug-Drug Interactions

Many patients with carcinoid syndrome or VIPomas being treated with Octreotide Acetate Injection s.c. have also been, or are being, treated with many other drugs to control the symptomatology or progression of the disease, generally without serious drug interaction.

Included are chemotherapeutic agents, H_2 antagonists, antimotility agents, drugs affecting glycemic states, solutions for electrolyte and fluid support or hyperalimentation, antihypertensive diuretics and anti-diarrheal agents.

Where symptoms are severe and OCTREOTIDE ACETATE OMEGA 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 Injection. Adjustment of the dosage of drugs, such as insulin, affecting glucose metabolism may be required following initiation of OCTREOTIDE ACETATE OMEGA therapy in patients with diabetes.

Since Octreotide Acetate Injection 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 Injection 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 Injection 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 analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by the CYP 3A4 and which have a low therapeutic index should therefore be used with caution (e.g. terfenadine, quinidine).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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

DOSAGE AND ADMINISTRATION

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.

Recommended Dose and Dosage Adjustment

OCTREOTIDE ACETATE OMEGA s.c. Single-use and Multidose Vials

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

Carcinoid Tumors

The suggested daily dosage of OCTREOTIDE ACETATE OMEGA during the first two weeks of therapy ranges from 100 to 600 µg per day in two to four divided doses (mean daily dosage is 300 µg). In the clinical studies, the median daily maintenance dosage was approximately 450 µg, but clinical and biochemical benefits were obtained in some patients with as little as 50 µg, while others required doses up to 1500 µg per day. However, experience with doses above 750 µg per day is limited.

VIPomas

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

Acromegaly

Daily dosages of 100 µg to 300 µg b.i.d. or t.i.d. are recommended at the beginning of treatment. Dosage adjustment should be based on monthly assessment of GH levels and

clinical symptoms, and on tolerability. In most patients, the optimal daily dose will be 200 to 300 µg per day. A maximum dose of 1500 µg should not be exceeded.
If no relevant reduction of GH levels and no improvement of clinical symptoms have been achieved within 3 months of starting treatment with OCTREOTIDE ACETATE OMEGA, therapy should be discontinued.

Prevention of Complications following Pancreatic Surgery
Daily dosage of 100 µg t.i.d., administered subcutaneously, for 7 consecutive days starting on the day of the operation at least one hour before laparatomy.

Bleeding Gastro-oesophageal Varices in patients with cirrhosis
The recommended dose of OCTREOTIDE ACETATE OMEGA is 25 µg/hour by continuous i.v. infusion for 48 hours. In patients with high risk of rebleeding, infusion should be maintained up to a maximum of 5 days.

Immediately prior to use, the contents of the single-use or multidose vial should be diluted in physiological saline. The volume of dilution will depend on the infusion system used and should be adjusted to ensure a continuous infusion of OCTREOTIDE ACETATE OMEGA at the recommended rate. Once diluted, the solution should be used within 24 hours. Discard unused portion.

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

Reconstitution:

Parenteral Products:

Solution for continuous i.v. infusion: Immediately prior to use, the contents of the single-use vial or multidose vial should be diluted in physiological saline. The volume of dilution will depend on the infusion system used and should be adjusted to ensure a continuous infusion of OCTREOTIDE ACETATE OMEGA at a rate of 25 µg/hour. The following are examples of dilutions which may be used:

OCTREOTIDE ACETATE OMEGA			Volume of physiological saline	Approximate available volume mL	Nominal Concentration µg/mL	Infusion rate mL/h (µg/h)
Concentration µg/mL	Size mL	Volume mL				
500	1	1	49	50	10	2.5 (25)
200	5	2.5	47.5	50	10	2.5 (25)
200	5	3	93	96	6.25	4 (25)

As with all parenteral drugs, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.
OCTREOTIDE ACETATE OMEGA diluted in physiological saline is stable for 24 hours when stored at room temperature. Discard unused portion.

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

OVERDOSAGE

OCTREOTIDE ACETATE OMEGA Single-use and Multidose Vials

A limited number of accidental overdoses of Octreotide Acetate Injection in adults and children have been reported. In adults, the doses ranged from 2,400-6,000 micrograms/day administered by continuous infusion (100-250 micrograms/hour) or subcutaneously (1,500 micrograms t.i.d.). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

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

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

The management of overdosage is symptomatic.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacokinetics

OCTREOTIDE ACETATE OMEGA s.c. Single-use and Multidose Vials
After subcutaneous (s.c.) injection of Octreotide Acetate Injection, octreotide acetate is rapidly and completely absorbed. Peak plasma concentrations are reached within 30 minutes. The half-life after subcutaneous administration is 100 minutes. After intravenous injection the elimination is biphasic with α and β half-lives of approximately 10 and 90 minutes, respectively. The volume of distribution is 0.4 L/kg body weight and the total body clearance is 160 mL/min. Plasma protein binding amounts to 65% with only negligible amounts bound to red blood cells.

STORAGE AND STABILITY

OCTREOTIDE ACETATE OMEGA s.c. Single-use and Multidose Vials

Single-use Vials:

For prolonged storage, OCTREOTIDE ACETATE OMEGA single-use vials should be kept at temperatures of 2 to 8ºC. Protect from light and from freezing.

For day-to-day use, the single-use vials may be stored at room temperature for up to 2 weeks; they must be protected from light. The single-use vials should be opened just prior to administration and any unused portion discarded.

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

Multidose Vials:

Store at 2 to 8ºC. Protect from light and from freezing.

For day-to-day use, the multidose vials (**OCTREOTIDE ACETATE OMEGA 200 µg/mL**) may be stored at room temperature for up to 2 weeks prior to initial puncture; they must be protected from light. After initial puncture, **OCTREOTIDE ACETATE OMEGA 200 µg/mL** multidose vials should be stored at temperatures of 2 to 8ºC and should be used within 15 days.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

OCTREOTIDE ACETATE OMEGA Single-use and Multidose Vials

OCTREOTIDE ACETATE OMEGA (octreotide acetate) is supplied in 2-mL vials, each containing 50, 100 or 500 µg in 1-mL of octreotide as acetate. OCTREOTIDE ACETATE OMEGA is available in boxes of 5 vials.

OCTREOTIDE ACETATE OMEGA is also available in 5 mL multidose vials. Each vial contains 1000 µg of octreotide as acetate (200 µg/mL).

Composition of OCTREOTIDE ACETATE OMEGA Single-Use Vials

Composition	Concentration[1] (µg/mL)		
Octreotide (free peptide*)	50	100	500
Glacial Acetic Acid	2000	2000	2000
Sodium Acetate Trihydrate	2000	2000	2000
Sodium Chloride	7000	7000	7000

[1]Water for Injection, q.s. 1.0 mL
* Present as octreotide acetate

Sodium acetate trihydrate or glacial Acetic acid is added to provide a buffered solution pH 4.2 ± 0.2.

Composition of OCTREOTIDE ACETATE OMEGA Multidose Vials

Composition	Concentration[1] (µg/mL)
Octreotide (free peptide*)	200
Glacial Acetic Acid	2000
Sodium Acetate Trihydrate	2000
Sodium Chloride	7000
Phenol	5000

1Water for Injection, q.s. 1.0 mL
* Present as octreotide acetate

Sodium acetate trihydrate or glacial Acetic acid is added to provide a buffered solution pH 4.2 ± 0.2.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

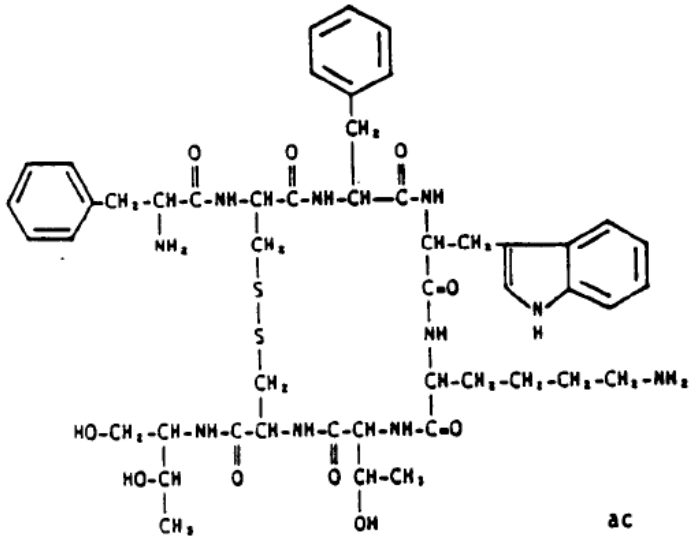
Drug Substance

Proper name: octreotide acetate

Chemical name: D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic(2→7) disulfide acetate

Molecular formula and molecular mass: $C_{49}H_{66}N_{10}O_{10}S_2$, x CH_3COOH, 1019.3 x 60.05

Structural formula:



Physicochemical properties:

Octreotide acetate is a bridged octapeptide analogue of somatostatin. It is a white to off-white amorphous lyophilisate, which melts with decomposition; it is very hygroscopic.

The values for pka (I) and pka (II) in water are 7.00 and 10.15 respectively. At 25°C, the solubility of octreotide acetate is >10 mg/mL in water; >10 mg/mL in glacial acetic acid and >10 mg/mL in methanol.

DETAILED PHARMACOLOGY

Pharmacodynamics

Pharmacodynamic studies with Octreotide Acetate Injection (octreotide acetate) in animals have shown that it inhibits secretion of basal and/or stimulated GH, insulin, glucagon in the rat and rhesus monkey and of gastric acid, and exocrine pancreatic enzymes in the rat, with greater potency than natural somatostatin. Octreotide acetate seems to possess some degree of specificity of pharmacological action in that it is much more potent in suppressing GH and glucagon levels than insulin levels when compared with somatostatin. In addition to its potency, Octreotide acetate has a long duration of action with respect to GH inhibition.

Octreotide acetate administration is associated with a minor fall of fasting plasma glucose in monkeys followed by a slight hypersecretion of glucose. In contrast, there occurs a postprandial hyperglycemia, most likely due to an inhibition of insulin.

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.

Pharmacokinetics

Pharmacokinetic studies have been performed in rats, dogs and rhesus monkeys after single and multiple doses. The bioavailability of Octreotide Acetate Injection after single subcutaneous (s.c.) injection in rats and dogs was approximately 100%. Highest concentrations were found in liver, kidneys, skin and lungs. Octreotide acetate was metabolized in the rat into smaller peptides, e.g. the dipeptide D-tryptophanlysine. However, as biliary and urinary excretion consisted mainly of unchanged drug, hepatic metabolism appeared slight. A biphasic elimination of octreotide acetate from plasma was also obtained with an α-disposition half-life of 0.3 to 0.4 hours and a β-phase between 1.2 and 3.2 hours. Multiple administrations did not change the pharmacokinetics of the drug compared to single administration.

In man, octreotide acetate is rapidly and completely absorbed after s.c. injection. Peak plasma concentrations reached after s.c. administration are about half of those obtained after intravenous (i.v.) administration of the same dose. Plasma protein binding is about 65%. The uptake in red blood cells is negligible. After i.v. administration there are two disposition half-lives, a short one of about 10 minutes and a longer one of about 1.5 hours. After s.c.

administration to healthy volunteers, the final disposition half-life is about 1.5 hours, the volume of distribution is 6 L and the total body clearance is about 160 mL/min. The absolute bioavailability of octreotide acetate calculated after s.c. administration was rather variable, with values of about 100% for 100 μg and about 130% for 50 μg and 200 μg. There is no significant accumulation under conditions of repeated s.c. administration.

Clinical Pharmacology

OCTREOTIDE ACETATE INJECTION s.c. Single-use and Multidose vials

Carcinoid Tumors

Patients with carcinoid tumors are the most responsive to therapy with approximately 70 to 90% achieving symptom control, characterized by a decrease in diarrhea and flushing. In many cases, this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid (5-HIAA). In the event of no beneficial response to Octreotide Acetate Injection treatment, continuation of therapy beyond one week is not recommended, although in non-responders no serious sustained adverse drug effects have been reported.

VIPomas

The biochemical characteristic of these tumors is over-production of vasoactive intestinal peptide (VIP). In 70% of patients with VIPomas, administration of Octreotide Acetate Injection results in alleviation of the severe secretory diarrhea typical of this condition and consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall to the normal reference range.

Acromegaly

In acromegalic patients (including those who have failed to respond to surgery, irradiation of dopamine agonist treatment), Octreotide Acetate Injection lowers plasma levels of GH and/or somatomedin C. A clinically relevant GH reduction (by 50% or more) occurs in almost all patients, and normalization (plasma GH < 5 ng/mL) can be achieved in about half the cases. In most patients, Octreotide Acetate Injection markedly reduces the clinical symptoms of the disease such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paresthesia. In patients with a large pituitary adenoma, Octreotide Acetate Injection treatment may result in some shrinkage of the tumor mass.

Prevention of complications following pancreatic surgery

Complications following high risk pancreatic surgery (such as peripancreatic fluid collection, abscess, leaking from the surgical anastomosis, fistula and subsequent sepsis and acute pancreatitis) are chiefly linked with pancreatic proenzyme secretion activated by surgical trauma.

They are due to pancreatic juice leaking from the pancreatic remnant and reaching the peripancreatic region. The action of the activated digestive enzymes leads to severe inflammation and may cause autodestruction of peripancreatic and pancreatic tissue, including intestinal organs and major vessels. Octreotide Acetate Injection inhibits basal and stimulated exocrine pancreatic secretion and, when administered peri- and post-operatively, reduces the incidence of complications following pancreatic surgery.

Bleeding Gastro-oesophageal varices

The precise mode of action of Octreotide Acetate Injection on portal hypertension is still unclear. Octreotide Acetate Injection 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.

TOXICOLOGY

ACUTE TOXICOLOGY

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

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

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

Subchronic and Chronic Toxicity

Species	Duration	Route	Dose (mg/kg/d)	Observations
Rats	4 weeks	i.p.	1.0, 4.0, 16.0	Low dose: Slightly↓ feed intake, slight ↑ in serum alkaline phosphatase (SAP) values Mid-dose: ↓ weight gain & feed intake, slight ↑ in urine volume & SAP, ↓ serum albumin High Dose: Moderate↓ in weight gain and feed intake, ↓ serum albumin, with slight ↑ in α_2-globulin, slight ↓ in serum glucose, slight ↑ in SGOT and SAP values, unilateral, small, soft testes in 2 M, inhibited spermiogenesis with atrophy of germinal epithelium of seminiferous tubules in 3M. NOAEL: 4mg/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 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 1M All groups: Additional investigation concentrating on determining the nature of the affected pituitary cell showed that octreotide acetate-treated recovery dogs stained positively for prolactin and negatively for growth hormone. Furthermore, plasma levels of prolactin, growth hormone and 17β estradiol were unaffected by octreotide acetate treatment.
Dogs	52 weeks	s.c.	0.24, 0.80, 1.25	Low and mid doses: ↓ lactate dehydrogenase (M) High dose: ↓ lactate dehydrogenase (M & F). 4 M died due to large tissue masses at the injection sites. All available information at present indicates that the findings are species-specific and have no significance to the use of Octreotide acetate in humans. All groups: ↓ body weight and body weight gain. Local irritation at the injection site (alopecia, encrustation and thickening/swelling of the skin). ↓ creatinine kinase and aspartate amino transferase. ↑alkaline phosphatases (F) and glucose; ↓ sodium levels; total protein, albumin and αglobulin; bilirubin and calcium (F).

Species	Duration	Route	Dose (mg/kg/d)	Observations
				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. 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 βphase 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 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.

Teratological and reproductive studies

Rats and rabbits were treated intravenously with Octreotide Acetate Injection (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 F_0 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 F_0 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 F_1 offspring was not affected except for some growth retardation. The reproduction performance of F_1 animals as well as the development of the F_2 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.

Mutagenicity

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 vehicle 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.

Oncogenicity Studies

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

Species	Duration	Route	N/dose	Dose (mg/kg/d)	Observations
Rats (KFM-han Wistar)	116 weeks	s.c.	60M 60F	Placebo, NaCl 0.9%, 0.24, 0.80, 1.25	Mid & high dose: Marginal but statistically significant ↑ in the relative proportion of lymphocytes by 10 to 8% on average in M of mid & high dose groups, and by 16% on average in F of high group, when compared with the controls. Dose-related ↓in body weight gain in F All groups: No treatment-related differences in 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 (KFM-han NMRI)	85/86 weeks (F) 98/99 weeks (M)	s.c.	60M 60F	Placebo, NaCl 0.9%, 0.1, 0.4, 1.2, 2.0	0.4, 1.2 & 2 mg/kg/d: ↑ incidence of duodenal mucosal hyperplasia (F) frequently associated with inflammation and duodenal dilatation. All treated-groups: No effect in 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.

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PART III: CONSUMER INFORMATION

Pr OCTREOTIDE ACETATE OMEGA
(Octreotide Acetate Injection)

This leaflet is part III of a three-part "Product Monograph" published when OCTREOTIDE ACETATE OMEGA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OCTREOTIDE ACETATE OMEGA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is OCTREOTIDE ACETATE OMEGA used for?

OCTREOTIDE ACETATE OMEGA (octreotide acetate) is used:

- to control symptoms in patients with gastroenteropancreatic (GEP) endocrine tumors or with acromegaly.
- for the prevention of complications following pancreatic surgery.
- for the emergency treatment of bleeding varices (stretched veins) in the esophagus and stomach in patients with liver disease and as protection from rebleeding.

What is a Gastroenteropancreatic (GEP) Endocrine Tumor?

GEP endocrine tumors are growths that have developed from endocrine cells in the gastrointestinal tract (the stomach, intestines, appendix) or the pancreas.

Some symptoms come about because GEP endocrine tumors produce and secrete chemical substances called peptides, i.e. small proteins in excess – overloading the system.

The over-secretion of peptides cause diarrhea and flushing.

Carcinoid tumors (generally occurring in the esophagus, stomach, intestines, appendix, and lungs) and VIPomas (almost always occurring in the pancreas) are the most common type of GEP endocrine tumor.

Diarrhea can cause dehydration, it is therefore very important to control it and replace the loss of water and electrolytes as quickly as possible.

What is Acromegaly?

Acromegaly is a life-time, uncommon, debilitating disease characterized by changes in facial bone structure and specific hormonal abnormalities.

Acromegaly is the result of an overproduction of growth hormone by the pituitary gland (a pea- sized gland located at the base of the brain). Uncontrolled disease may lead to arthritis, cardiac and neurologic problems. Approximately 20% to 30% of acromegalic patients also demonstrate high blood pressure.

What OCTREOTIDE ACETATE OMEGA (octreotide acetate) Does?

GEP Endocrine Tumors:
OCTREOTIDE ACETATE OMEGA works to help slow down the release of the peptides that cause diarrhea and flushing. It also stimulates water absorption.

Acromegaly:
Octreotide Acetate Injection has been shown to lower the overproduction of growth hormone by the pituitary gland.

When it should not be used:

OCTREOTIDE ACETATE OMEGA should not be used if you are allergic to the active ingredient octreotide or to any other ingredient of the formulation.

What the medicinal ingredient is:

octreotide acetate.

What the important nonmedicinal ingredients are:

The single-use vials contain: glacial acetic acid, sodium acetate trihydrate, sodium chloride and water for injection.
The multidose vials contain: glacial acetic acid, sodium acetate trihydrate, sodium chloride, phenol and water for injection.

What dosage forms it comes in:

OCTREOTIDE ACETATE OMEGA (octreotide acetate) is a solution supplied in:

- 1 mL vials, each containing 50 µg, 100 µg or 500 µg of octreotide as acetate. OCTREOTIDE ACETATE OMEGA is available in boxes of 5 vials.

and

- 5 mL multidose vials. Each vial contains 1000 µg of octreotide as acetate (200 µg/mL).

WARNINGS AND PRECAUTIONS

BEFORE you use OCTREOTIDE ACETATE OMEGA talk to your doctor or pharmacist if you:

- have high blood pressure (hypertension),
- have problems with your blood sugar levels, either too high or too low (hypoglycaemia),
- have gallstones or have had gallstones in the past, as prolonged use of OCTREOTIDE ACETATE OMEGA may result in gallstone formation,
- have problems with your liver (e.g. liver cirrhosis),
- have problems with your kidneys and require dialysis,

- are pregnant, suspect that you may be pregnant,
- are breast feeding,
- have heart problems.

If you receive long treatment with OCTREOTIDE ACETATE OMEGA your doctor may wish to check your thyroid function periodically.

There is very little experience with the use of OCTREOTIDE ACETATE OMEGA in children.

Women of child-bearing potential should use an effective contraceptive method during treatment.

INTERACTION WITH THIS MEDICATION

Drugs that may interact with OCTREOTIDE ACETATE OMEGA include:

- 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)

Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription.

OCTREOTIDE ACETATE OMEGA is best injected between meals or on retiring to bed. This may reduce the gastrointestinal side effects of OCTREOTIDE ACETATE OMEGA.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will tell you how much OCTREOTIDE ACETATE OMEGA to take each day. OCTREOTIDE ACETATE OMEGA is to be injected under your skin (subcutaneous injection). The doctor will also tell you how to divide your dosage through the day.

How to Prepare Your Injection of OCTREOTIDE ACETATE OMEGA?

You will receive your supply of OCTREOTIDE ACETATE OMEGA either in single-use or multidose vials. The single-use or multidose vials should be visually inspected and not used in the presence of floating particles or discoloration.

Single-use and Multidose Vials

1. Peel off the aluminum seal.
2. Wipe the top of the vial with an alcohol swab.
3. Remove the cap from the needle and insert the needle into the vial through the rubber stopper.
4. Leave the needle in the bottle.
5. Turn the vial and the syringe upside down. Keep the needle tip within the liquid. Pull the plunger and carefully withdraw the prescribed amount of OCTREOTIDE ACETATE OMEGA (your doctor or nurse will tell you how to read the markings on the syringe so that you fill it with the correct amount of drug for your dose).
6. Turn the bottle and syringe back upright.
7. Withdraw the needle from the vial.
8. Check to see if there are any air bubbles in the syringe. If bubbles do appear, hold the syringe upright (with the needle pointed up) and lightly tap the barrel. This should make the bubbles rise to the top of the syringe. Then gently press the plunger to push the bubbles out.

How to Inject Your Dose of OCTREOTIDE ACETATE OMEGA

1. Choose the area of your hip, thigh, or abdomen where you want to make your injection.
2. Clean the site with a fresh alcohol wipe, and keep it nearby.
3. Hold the syringe like a pencil, and remove the needle cap.
4. Use the thumb and forefinger of your other hand to gently pinch up a fold of skin at the place you want to inject. This will lift the subcutaneous tissue away from the muscle underneath.
5. Hold the syringe at a 45° angle, and insert the entire length of the needle into the fold of skin in one quick motion.
6. Once the needle is inserted, let go of the skin.
7. Using your free hand, pull back on the plunger slightly to check whether you have placed the needle in a blood vessel. (You don't want to.) If any blood appears in the syringe, this is not a proper site for your injection. You will have to remove and discard the syringe and needle and start over.
8. Once the needle is inserted properly, slowly inject all of the medication.
9. When you are finished injecting the medicine, place your alcohol wipe where the needle enters the skin. Press lightly.
10. Withdraw the needle at the same angle it is inserted.
11. Gently hold the wipe on your skin for about five seconds.
12. Put the cap back on the needle and dispose of the syringe and needle safely. Do not reuse the syringe and needle. Single-use syringes and needles are used to reduce the chance of infection. Collect your used needles and syringes in a metal container, such as a coffee can, and

then dispose of them in a covered garbage can. This will keep others (especially children) from injuring themselves.

Important Points to Remember
Pay close attention to the amount of drug you are taking into the syringe for injection. Make sure it is the amount your doctor has prescribed for you.

Missed Dose:

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

Overdose:

No life-threatening reactions have been reported after overdosage of OCTREOTIDE ACETATE OMEGA.

If you think you have injected more OCTREOTIDE ACETATE OMEGA than you should, contact your doctor or poison control center in your area.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines OCTREOTIDE ACETATE OMEGA may cause some side effects. If you experience any of these, tell your doctor.

Some patients have experienced a burning sensation at the injection site. For most people, the burning lasts only a few moments. Injecting the drug at room temperature rather than cold from the refrigerator may alleviate the burning sensation.

Serious side effects

- Gallstones, leading to sudden back pain.
- Too much or too little sugar in the blood.
- Underactive thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight; tiredness, feeling cold, or swelling at the front of the neck.
- Changes in thyroid function tests.
- Inflammation of the gallbladder (cholecystitis).
- Impaired glucose tolerance.
- Irregular heart beat (slow or fast).
- Thirst, low urine output, dark urine, dry flushed skin.
- Hypersensitivity (allergic) reactions including skin rash.
- A type of an allergic reaction (anaphylaxis) which causes difficulty in breathing, swelling of the face or dizziness.
- Acute inflammation of the pancreas gland causing severe stomach pain (pancreatitis).
- 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.

Other side effects

The side effects listed below are usually mild and tend to disappear as treatment progresses.

- nausea
- vomiting
- stomach pain
- diarrhea
- feeling of fullness in the stomach
- flatulence (wind)
- loss of appetite
- constipation
- headache
- stomach discomfort after meal
- fatty stools
- loose stools
- discoloration of faeces
- dizziness
- change in liver function tests
- hair loss
- shortness of breath.

Since gallstones may occasionally form during prolonged use of OCTREOTIDE ACETATE OMEGA, your doctor may wish to check your gallbladder periodically.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Your medication should be withheld or stopped. Talk with your doctor.
		Only if severe	In all cases	
Common	- Formation of gallstones in the gallbladder (severe pain in the upper right abdomen which may last for several hours, particularly after a fatty meal, possible nausea or vomiting)		√	
Uncommon	- Acute pancreatitis (inflammation of the pancreas gland causing severe stomach pain)			√
	- Allergic reaction (anaphylaxis) to Octreotide Acetate Injection (difficulty in breathing, dizziness, swelling of the			√

	face, and skin rash)			
	- Diabetes (symptoms include unusual thirst, frequent urination, extreme fatigue or lack of energy, tingling or numbness in the hands or feet)		√	
	- 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.		√	
	- Irregular heart beat (slow or fast)		√	

This is not a complete list of side effects. For any unexpected effects while taking OCTREOTIDE ACETATE OMEGA, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

OCTREOTIDE ACETATE OMEGA must be stored at 2° to 8°C (in a refrigerator). However, you may leave your daily dose of OCTREOTIDE ACETATE OMEGA (single-use or multidose vials) out at a room temperature of up to 30°C for up to 2 weeks. The single-use vials should be opened just prior to administration and any unused portion **discarded**.

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

Do not use OCTREOTIDE ACETATE OMEGA (single-use or multidose vials) after the expiry date.
Keep in a safe place out of reach of children and pets.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Omega Laboratories, Ltd., at:

Montreal: (514) 335-0310 or
1-800-363-0584
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