PRODUCT MONOGRAPH

PrOCPHYL™

(Octreotide Injection)

50 μg/mL, 100 μg/mL and 500 μg/mL
octreotide (as octreotide acetate) per 1 mL pre-filled syringe

STERILE

Synthetic Octapeptide Analogue of Somatostatin

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Table of Contents

PrOCPHYL™

(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 dose pre-filled syringes (1 mL): 50 μg/mL, 100 μg/mL or 500 μg/mL	lactic acid, sodium chloride, sodium hydroxide (used for pH adjustment)

INDICATIONS AND CLINICAL USE

General

OCPHYL (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 OCPHYL decreases the size, rate of growth, or development of metastases in patients with these tumors.

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

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

Carcinoid Tumors

OCPHYL 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)

OCPHYL 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 results in improvement in electrolyte abnormalities, e.g. hypokalemia, often enabling reduction of fluid and electrolyte support.

Acromegaly

OCPHYL 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 OCPHYL 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 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, OCPHYL treatment may result in some shrinkage of the tumor mass.

Prevention of Complications following Pancreatic Surgery

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

Bleeding Gastro-oesophageal Varices

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

CONTRAINDICATIONS

OCPHYL (octreotide acetate) is contraindicated in patients with a known hypersensitivity to octreotide or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

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

As GH-secreting pituitary tumors may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients treated with octreotide acetate injection subcutaneous (s.c.) be carefully monitored. If evidence of tumor 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 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 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 were 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 OCPHYL.

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 OCPHYL.

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. 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 B_{12} 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 gastrointestinal (G.I.) tract in patients with conditions producing such a loss. If such patients are receiving total

parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

Hepatic/Biliary/Pancreatic

Gallbladder and Related Events

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

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during octreotide acetate injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

It is recommended that patients on extended therapy with octreotide acetate injection 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 injection 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 injection technique should be given to the patients and to other persons who may administer OCPHYL (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 OCPHYL treatment.

Pediatrics: Experience with octreotide acetate injection 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 injection of OCPHYL. Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of octreotide 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 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 Injections s.c. 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 Injections

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
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

Table 1 Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumor Patients and 114 Acromegalic Patients Treated with Octreotide Acetate Injections

Adverse Reaction Profile According to Body System	GEP Endocrine Tumor Patients (n=196) %	Acromegalic Patients (n=114) %
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
Prostatitis	-	1.8
Tumor breast	-	1.8
Hematologic		
Hematoma, injection site	-	9.6

Table 1 Composite Listing of Adverse Reactions in 196 GEP Endocrine Tumor Patients and 114 Acromegalic Patients Treated with Octreotide Acetate Injections

Adverse Reaction Profile According to Body System	GEP Endocrine Tumor Patients (n=196) %	Acromegalic Patients (n=114) %
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 include pain and sensations of stinging, tingling or burning at the site of injection, with redness and swelling. These rarely last more than fifteen minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection and by slowly injecting octreotide acetate.

In clinical trials, acromegalic patients had a higher incidence of 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 injection s.c. treatment.

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

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

Specific Adverse Event by Body System	Placebo B301 (n=55)%	Octreotide Acetate B301 (n=60)%	Octreotide Acetate B301, B302 & B303 (n=114)%
Skin			
Pain at injection site	2 (3.6)	5 (8.3)	11 (9.6)
Acne	--	2 (3.3)	5 (4.4)
Bruise	1 (1.1)	2 (3.3)	5 (4.4)
Pruritus	--	--	5 (4.4)
Alopecia/Baldness/Hair loss	--	--	4 (3.5)

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

Specific Adverse Event by Body System	Placebo B301 (n=55)%	Octreotide Acetate B301 (n=60)%	Octreotide Acetate B301, B302 & B303 (n=114)%
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. 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 in Bleeding Gastro-oesophageal Varices

Raised blood glucose levels were reported in 23 of 98 cirrhotic patients treated with octreotide acetate 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.

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

Pscyhiatric: 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

Carcinoid Tumors

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 in this group and included abdominal pain, diarrhea (loose stools), constipation, flatulence, nausea and vomiting.

General

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.

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

Because of its inhibitory action on growth hormone, glucagon and insulin, octreotide acetate injection 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 s.c.

Rarely, hypersensitivity reactions have been reported.

Isolated reports of anaphylactic reaction have been reported. Octreotide acetate administered s.c. and to a much lesser degree by i.v. infusion, can lead to hypersensitivity reaction that may range from generalized priritus 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 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 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 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 therapy in patients with diabetes.

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 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

OCPHYL s.c. Single Dose Pre-filled Syringes

Subcutaneous injection is the recommended route of administration of OCPHYL 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 OCPHYL 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 OCPHYL, 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 OCPHYL 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 pre-filled syringes 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 OCPHYL 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

Solution for continuous i.v. infusion: Immediately prior to use, the contents of the pre-filled syringe 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 OCPHYL at a rate of 25 µg/hour. The following are examples of dilutions which may be used:

OCPHYL			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)
500	1	1	79	80	6.25	4 (25)
100	1	1	15	16	6.25	4 (25)

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

OCPHYL diluted in sterile physiological saline is stable for 24 hours at room temperature. Discard unused portion.

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

OVERDOSAGE

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

A limited number of accidental overdoses of octreotide acetate in adults and children have been reported. In adults, the doses ranged from 2,400-6,000 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 at doses of 3,000-30,000 micrograms/day in divided doses subcutaneously.

The management of overdosage is symptomatic.

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

After subcutaneous (s.c.) injection of 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

Pre-filled Syringes

OCPHYL pre-filled syringes must be stored at 2 to 8ºC. Keep container in the outer carton in order to protect from light. Do not freeze.

When OCPHYL is used daily by patients, the pre-filled syringes may be stored at room temperature for up to 2 weeks, protected from light. The pre-filled syringes should be opened just prior to administration.

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

For the storage conditions of diluted solution, please see DOSAGE AND ADMINISTRATION, Reconstitution.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OCPHYL (octreotide acetate) is supplied in a 1 mL single dose syringe with a fixed 27 gauge ½ inch non-interchangeable needle, containing 50, 100 or 500 µg of octreotide (as octreotide acetate). OCPHYL is available in boxes of 5 pre-filled syringes. Each syringe plunger is colour coded according to the dose: red (50 µg), yellow (100 µg), and blue (500 µg).

Composition of OCPHYL Pre-filled Syringes

Composition	**Concentration[1] (µg/mL)**		
Octreotide (free peptide)[*]	50	100	500
Lactic acid	3,000	3,000	3,000
Sodium chloride	7,000	7,000	7,000

Lactic acid and sodium hydroxide are added to provide a buffered solution, pH range 3.9 to 4.5

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

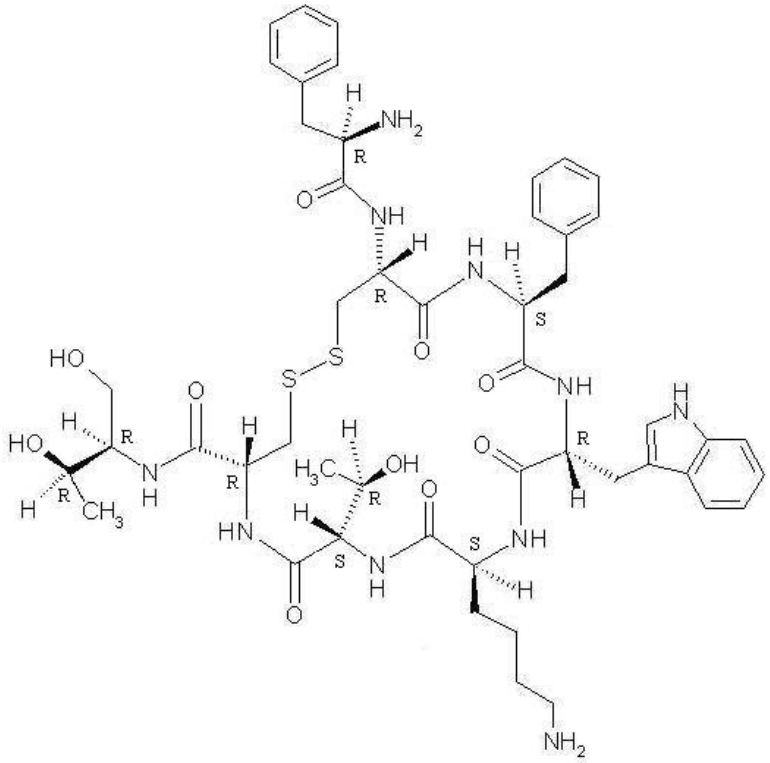
Proper name: octreotide acetate

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: Free Peptide: $C_{49}H_{66}N_{10}O_{10}S_2$
Acetate Salt: $C_{49}H_{66}N_{10}O_{10}S_2$ *n CH_3COOH; $1 \leq n \leq 2$

Molecular mass: 1019.3 g/mol as free peptide

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 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 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

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 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 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 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 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 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 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 on portal hypertension is still unclear. Octreotide acetate 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 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 α2-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.

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

REFERENCES

1. Anderson JV, Bloom SR. Long term therapy with a somatostatin derivative (SMS 201-995) in a series of patients with vasoactive intestinal peptide secreting pancreatic tumors. Can J Physiol Pharmacol 1986; 64 (suppl): 9, abstr no 119.

2. Bassi Cl, Falconi M, *et al*. Prophylaxis of Complications after Pancreatic Surgery: Results of a Multicentre trial in Italy. Digestion. 1994; **55** (Suppl. 1): 41-47.

3. Besson I, Ingrand P, *et al*. Sclerotherapy with or without octreotide for acute variceal bleeding. N. Engl. J. Med. 1995; 333: 555-560

4. Bloom SR, Greenwood C (ed.). Proceedings of somatostatin '85: Chemical, Physiological and Clinical advances. Scand J, Gastroenterology 1986; 21(S119):1-274.

5. Brabant G, Muller MJ, Rotsch M, *et al*. Treatment of carcinoid syndrome and VIPoma with a long-acting somatostatin derivative (SMS 201-995). Scand J Gastroenterol 1986; 21 (suppl 119): 177-180.

6. Büchler M, Freiss H, *et al.* Role of Octreotide in the Prevention of Postoperative Complications Following Pancreatic Resection. Am. J. Pancreatic Surgery. 1992; 163: 125- 131.

7. Clements D, Elias E. Regression of metastatic VIPoma with somatostatin derivative SMS 201-995. Lancet 1985; I (8433): 874-5.

8. Del Pozo E, Kutz K. SMS 201-995, a new somatostatin analog: pharmacological profile. Neuroendocrinol Lett 1985; 7:111.

9. Del Pozo E, Neufeld M, Schlüter K, Tortosa F, Clarenbach P, Bieder E, Wendel L, Nüesch E, Marbach P, Cramer H, *et al.* Endocrine profile of a long-acting somatostatin derivative SMS 201-995. Study in normal volunteers following subcutaneous administration. ACTA Endocrinol (COPENH) 1986; III(4):433-9.

10. Dimeck J, Feniuk W, et al. Somatostatin-induced contraction of human isolated saphenous vein involves sst2 receptor-mediated activation of L-type calcium channels. J Cardiovasc Pharmacol 1995; 26: 721-728.

11. Edwards CA, Cann PA, Read NW, et al. Effect of somatostatin derivative SMS 201-995 on fluid and electrolyte transport in a patient with secretory diarrhea. Scand J Gastroenterol 1986; 21 (suppl 119): 259-261.

12. Friess H, Klempa I, *et al.* Prophylaxis of Complications after Pancreatic Surgery: Results of a Multicentre trial in Germany. Digestion. 1994; 55(Suppl. 1): 35-40.

13. Hwang SJ, Lin HC, *et al*. A randomized controlled trial comparing octreotide and vasopressin in the management of acute esophageal variceal bleeding. J Hepatology 1992, 16: 320-325.

14. Juby LD, Burke DA, Axon ATR. Somatostatin derivative SMS 201-995 long term therapy for VIPoma. Postgrad Med J 1987; 63: 287-289.

15. Kallivretakis N, Yotis A, del Pozo E, Marbach P, Mountokalakis T, Tolis G. Pharmacokinetics of SMS 201-995 in normal subjects and in patients with severe renal failure. Neuroendocrinol Lett 1985; 7:92:Be 3.2.

16. Kraenzlin ME, Wood SM, Neufeld M, Adrian TE, Bloom SR. Effect of long acting somatostatin-derivative, SMS 201-995, on gut hormone secretion in normal subjects. Experientia (Basel) 1985; 41:738-40.

17. Kraenzlin ME, Chang JLC, Wood SM, *et al.* Long-term treatment of a VIPoma with somatostatin derivative resulting in remission of symptoms and possible shrinkage of metastases. Gastroenterology 1985; 88: 185-187.

18. Kvols LK, Moertel CE, O'Connel MJ, Schutt AL, Rubin, Hahn RG. Treatment of malignant carcinoid syndrome: evaluation of a long acting somatostatin derivative. New Engl J Med 1986; 315(II):663-6.

19. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin derivative. New Engl J Med 1985; 313:1229-30.

20. Long RG, Barnes AJ, Adrian TE, Mallinson CN, Brown MR, Vale W, Rivier JE, Christofides ND, Bloom SR. Suppression of pancreatic endocrine tumour secretion by long-acting somatostatin derivative. Lancet 1979; ii:764-7.

21. Marsh HM, Martin JK, Kvols LK, *et al.* Carcinoid crisis during anesthesia: Successful treatment with somatostatin derivative. Anesthesiology 1987; 66: 89-91.

22. Pederzoli P, Bassi C, et al. Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. Br. J. Surgery. 1194; 81: 265-269.

23. Pedretti G, Elia G, *et al.* Octreotide *versus* terlipressin in acute variceal hemorrhage in liver cirrhosis. Emergency control and prevention of early rebleeding. Clin. Invest. 1994; 72: 653- 659.

24. Santagelo W, O'Dorisio T, Kim J, Severino G, Krejs G. VIPoma syndrome: effect of a somatostatin derivative on intestinal water and ion transport. Regul Pept 1985; S53.

25. Souquet JC, Charvialle JA *et al.* Biological and clinical efficacy of a long-acting somatostatin analog (SMS 201-995) in secreting apudomas. Can J Physiol Pharmacol 1986; 64 (suppl): 64 (Abstr. No. 240).

26. Stoeckmann F, Richter G, Conlon JM, *et al.* Effect of short- and long-term treatment with SMS 201-995 in patients with carcinoid tumors. Gastroenterology 1986; 90: 1650.

27. Stoeckmann F, Creutzfeldt W. SMS 201-995 for treatment of patients with carcinoid tumors and Zollinger-Ellison syndrome. Regul Pept 1987; 18: 377.

28. Stoeckmann F, Richter G, Lembcke B, *et al.* Long-term treatment of patients with endocrine gastrointestinal tumours with the somatostatin derivative SMS 201-995. Scand J Gastroenterol 1986; 21 (suppl 119); 230-237.

29. Sung JJY, Chung S, *et al.* Octreotide infusion or emergency sclerotherapy for variceal haemorrhage. Lancet 1993; 342: 637-641.

30. Sung JJY, Chung S, et al. Prospective randomized study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. Lancet 1995: 346: 1666-1669.

31. Vinik AI, Tsai ST, Moattari AR, *et al.* Somatostatin derivative (SMS 201-995) in the management of gastroenteropancreatic tumors and diarrhea syndromes. Amer J Med 1986; 81 (suppl 6B); 23-40.

32. Chanson P. et al. Octreotide Therapy for Thyroid-Stimulating Hormone Secreting Pituitary Adenomas. Ann. of Inter. Med. 1993, Vol. 119; p. 236-240.

33. Ginsburg J. Concensus Discussion and Conclusions. In Sandostatin and the Treatment of Acromegaly, Concensus Round Table, Amsterdam 1987 - Edit.: S. Lamberts. Publ. Springer Verlag Berlin, Heidelberg, New York, London, Paris, Tokyo 1988 p. 163-171.

34. Papagrigoriou L. *et al.* Administration of Octreotide in Acromegaly. J. Endocr. Invest. 1993, Vol.16, Suppl.8, p.140, Abs. A 43).

35. Roelen C. *et al.* High Affinity Growth Hormone Binding Protein in Plasma of Patients with Acromegaly and the Effect of Octreotide Treatment. Clin.Endocr. 1991, Vol.37, p.373-378.

36. Schindel B. *et al.* Effect of Octreotide on 24-hour Growth Hormone and Prolactin Secretory Patterns in Acromegalies. Hormone Research 1991, Vol.36, p. 209-215.

37. [Pr]SANDOSTATIN Product Monograph, Novartis Pharmaceuticals Canada Inc. Date of Revision: September 3, 2009, Submission Control No: 130761.

PART III: CONSUMER INFORMATION

PrOCPHYL™
(octreotide acetate injection)

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

ABOUT THIS MEDICATION

What OCPHYL is used for:

OCPHYL (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 causes 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 OCPHYL (octreotide acetate) does:

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

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

When it should not be used:

OCPHYL 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 dose syringes contain: lactic acid, sodium chloride, sodium hydroxide and water for injection.

What dosage forms it comes in:

OCPHYL (octreotide acetate) is a solution supplied in:

- 1 mL single dose syringes, each containing 50 μg, 100 μg or 500 μg of octreotide (as octreotide acetate). OCPHYL is available in boxes of 5 syringes.
- Each syringe plunger is colour coded according to the dose: red (50 μg), yellow (100 μg), and blue (500 μg).

WARNINGS AND PRECAUTIONS

BEFORE you use OCPHYL 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 OCPHYL 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 OCPHYL your doctor may wish to check your thyroid function periodically.

There is very little experience with the use of octreotide acetate in children.

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with OCPHYL 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.

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

PROPER USE OF THIS MEDICATION

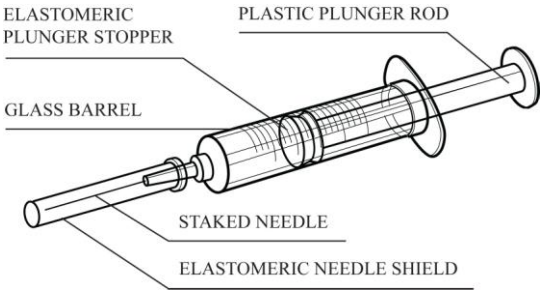
Usual dose:

Your doctor will tell you how much OCPHYL to take each day. OCPHYL is to be injected under your skin (subcutaneous injection). Your doctor will also tell you how to divide your dosage throughout the day.

Directions for use

YOUR DOCTOR WILL SHOW YOU HOW TO INJECT YOURSELF WITH OCPHYL. IT IS VERY IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS CAREFULLY. IF THERE IS ANYTHING YOU DO NOT UNDERSTAND OR WOULD LIKE CLARIFIED, ASK YOUR DOCTOR OR NURSE FOR MORE INFORMATION SO YOU ARE COMFORTABLE SELF-ADMINISTERING OCPHYL AT HOME.

OCPHYL is available in ready-to-use, single-dose, pre-filled syringes.



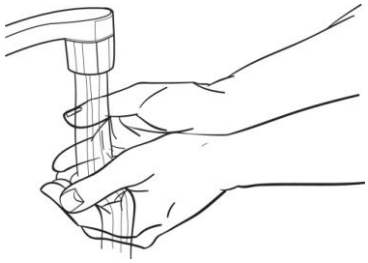
Each pre-filled syringe contains enough octreotide (as octreotide acetate) for one injection. Avoid pressing on the syringe plunger rod before use not to lose any contents of the syringe.

Caution

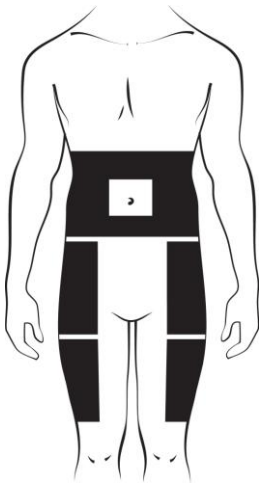
- Always work on a clean, flat surface.
- Do not remove the safety cap until ready to use. The needle must not touch any surface except alcohol-cleaned skin.
- Local discomfort may be reduced by allowing the solution to reach room temperature prior to injection and injecting OCPHYL slowly. Do not warm artificially.
- Always check that you have the right product before injecting. The label on the pre-filled syringe should read OCPHYL. The dosage strength on the pre-filled syringe should be the dose prescribed by your doctor.
- Always check the expiration date before use. Never use a pre-filled OCPHYL syringe after the expiration date indicated on the label.
- The OCPHYL liquid in the pre-filled syringe should be visually inspected before use. It should be clear and colourless. Do not use OCPHYL if the solution looks discoloured or cloudy or if particles are present. Any defective pre-filled syringe should be discarded.

1. Gather everything you need on a clean work surface:
    - One OCPHYL pre-filled syringe in its wrapping
    - Alcohol pads (not supplied with the product)
    - A puncture-proof container for disposal of used needles (ask your pharmacist for a proper sharps container)

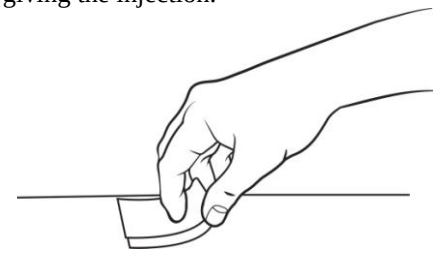
2. Wash your hands with soap and warm water.



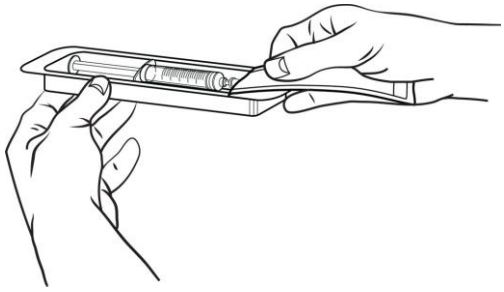
3. Choose the area of your hip, thigh, or abdomen (at least 5 cm away from your belly button) where you want to inject. Make sure you change sites each time you inject OCPHYL. The diagram below shows the recommended subcutaneous injection sites.



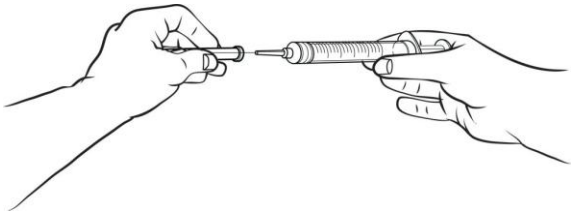
4. Using an alcohol pad, clean an area of skin approximately 5 cm x 5 cm at the injection site and allow the alcohol to dry. DO NOT touch this area again before giving the injection.



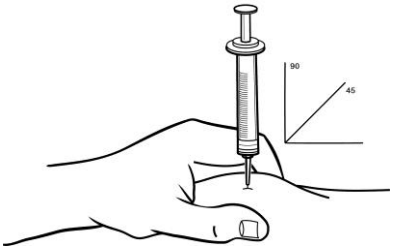
5. Remove the OCPHYL syringe from its wrapping by completely peeling off the backing from the blister packaging and then pick up the syringe by its glass barrel.



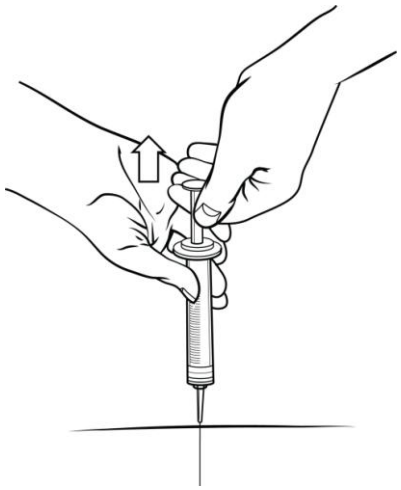
6. Holding the syringe like a pencil, carefully pull the needle cover straight off.



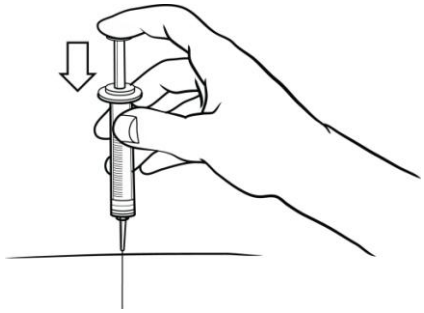
7. Invert the syringe and hold it like a dart. Use the thumb and forefinger of your other hand to gently pinch a fold of cleaned skin at the injection site. This will lift the subcutaneous tissue away from the muscle underneath. Hold the syringe at a 45- or 90-degree angle, and, in one quick motion, insert the entire length of the needle into the fold of skin.



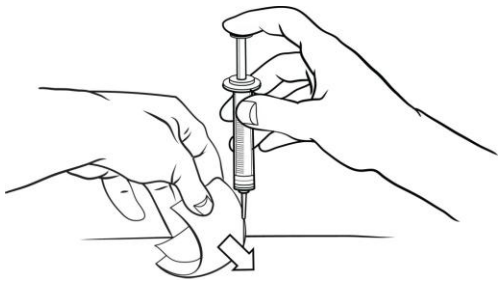
8. Once the needle is inserted, let go of the skin. Using your free hand, slightly pull back on the plunger to check whether you have placed the needle in a blood vessel. If any blood appears in the syringe, this is not a proper injection site. You will have to remove the needle, discard the syringe and start over at step 3 using a new syringe.



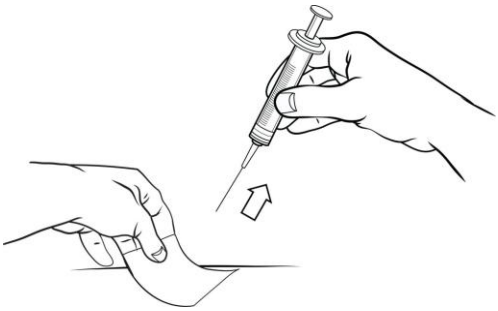
9. When the needle is inserted in a proper injection site, slowly inject the entire contents of the pre-filled syringe.



10. When you are finished injecting OCPHYL, place cotton swab where the needle enters the skin and press lightly.

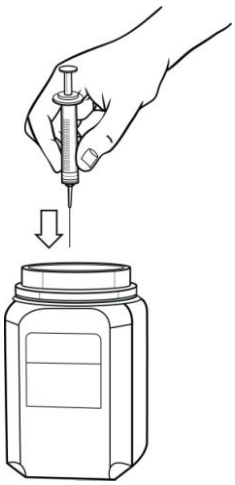


11. Withdraw the needle at the same angle that it was inserted.



12. Gently hold the cotton swab on the injection site for a minimum of 5 to 10 seconds.

13. **If you have a puncture-proof container (preferred):**
Do not reuse the pre-filled syringe. Do not try to put the safety cap back onto the needle. Dispose of the syringe in your puncture-proof container immediately after use. When the needle disposal container is full, take the container to a clinic or pharmacy for proper disposal.



If you do not have a puncture-proof container:
Do not reuse the pre-filled syringe. Put the safety cap back onto the needle very carefully, and dispose of the syringe safely. Collect your used syringes in a metal container. When the container is full, close it tightly, and take it to a clinic or pharmacy for proper disposal.

Missed Dose:

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

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

No life-threatening reactions have been reported after overdosage of octreotide acetate.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines OCPHYL 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 OCPHYL, 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		Stop taking drug and call your doctor or pharmacist
		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 (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)		√	

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
- 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 OCPHYL, contact your doctor or pharmacist.

HOW TO STORE IT

OCPHYL pre-filled syringes must be stored at 2°C to 8°C (in a refrigerator). Keep container in the outer carton in order to protect from light. Do not freeze.

When OCPHYL is used daily by patients, the pre-filled syringes may be stored at room temperature for up to 2 weeks, protected from light.
The pre-filled syringes should be opened just prior to administration.

Do not use OCPHYL after the expiry date.

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

REPORTING SUSPECTED SIDE EFFECTS

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 0701E
    Ottawa, Ontario
    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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, PENDOPHARM, Division of Pharmascience Inc., at:
1 888 550-6060.

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H4P 2T4

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