

## PRODUCT MONOGRAPH

**Pr SOMAVERT\***

pegvisomant for injection

10, 15, 20, 25 and 30 mg per vial

GH Receptor Antagonist

Pfizer Canada ULC  
17,300 Trans-Canada Highway  
Kirkland, Quebec H9J 2M5

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# PrSOMAVERT\*

pegvisomant for injection

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	lyophilized powder, 10, 15, 20, 25 and 30 mg per vial in package that also includes diluent (Sterile Water for Injection, Ph. Eur.) in a vial or pre-filled syringe	None  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

**SOMAVERT** (pegvisomant for injection) is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery, and/or radiation therapy or for whom these therapies are not appropriate. The goal of treatment is to normalize serum insulin-like growth factor-I (IGF-I) levels and to improve clinical signs and symptoms.

**Geriatrics** ( $\geq 65$  years of age): There is limited information in patients over 65 years of age (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

**Pediatrics** ( $< 18$  years of age): The safety and effectiveness of **SOMAVERT** in pediatric patients have not been established.

### CONTRAINDICATIONS

**SOMAVERT** (pegvisomant for injection) is contraindicated in patients with a history of hypersensitivity to any of its components. The stoppers on the vial of **SOMAVERT** and the vial of diluent are latex free.

## WARNINGS AND PRECAUTIONS

### General

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids (see **DRUG INTERACTIONS, Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

### **Tumor Growth**

Tumors that secrete growth hormone (GH) may expand and cause serious complications. Therefore, all patients with these tumors, including those who are receiving **SOMAVERT** (pegvisomant for injection), should be carefully monitored with periodic imaging scans of the sella turcica. During clinical studies of **SOMAVERT**, two patients manifested progressive tumor growth. Both patients had, at baseline, large globular tumors impinging on the optic chiasm, which had been relatively resistant to previous anti-acromegalic therapies. Overall, mean tumor size was unchanged during the course of treatment with **SOMAVERT** in the clinical studies.

### **Information for Patients**

Patients and any other persons who may administer **SOMAVERT** should be carefully instructed by a health care professional on how to properly reconstitute and inject the product (see **PART III: CONSUMER INFORMATION**). No studies on the effect on the ability to drive and use machines have been performed.

Patients should be informed about the need for serial monitoring of liver enzyme tests, and told to discontinue therapy and contact their physician if they become jaundiced immediately. In addition, patients should be made aware that serial IGF-I levels will need to be obtained to allow their physician to properly adjust the dose of **SOMAVERT**.

### Endocrine and Metabolism

#### **Glucose Metabolism**

GH opposes the effects of insulin on carbohydrate metabolism by decreasing insulin sensitivity; thus, glucose tolerance may increase in some patients treated with **SOMAVERT**. Although no clinically relevant hypoglycemia was observed during clinical trials among acromegalic patients with diabetes treated with **SOMAVERT**, these patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary (see **DRUG INTERACTIONS, Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

#### **GH Deficiency**

**SOMAVERT** is a potent antagonist of GH action. A state of functional GH deficiency may result from administration of **SOMAVERT**, despite the presence of elevated serum GH levels. During treatment with **SOMAVERT**, patients should be carefully observed for clinical signs and symptoms of a GH-deficient state. Dose adjustments of **SOMAVERT** should be made to maintain serum IGF-I concentrations within the age-adjusted normal range.

## **Hepatic/Biliary/Pancreatic**

### **Liver Tests (LTs)**

Elevations of serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 10 times the upper limit of normal (ULN) were reported in two patients (0.8%) treated with **SOMAVERT** during pre-marketing clinical studies. One patient was rechallenged with **SOMAVERT**, and the recurrence of elevated transaminase levels suggested a probable causal relationship between administration of the drug and the elevation in liver enzymes. A liver biopsy performed on the second patient was consistent with chronic hepatitis of unknown etiology. In both patients, the transaminase elevations normalized after discontinuation of the drug.

During the pre-marketing clinical studies, the incidence of elevations in ALT greater than 3 times but less than or equal to 10 times the ULN in patients treated with **SOMAVERT** and placebo were 1.2% and 2.1%, respectively.

Elevations in ALT and AST levels were not associated with increased levels of serum total bilirubin (TBIL) and alkaline phosphatase (ALP), with the exception of two patients with minimal associated increases in ALP levels (i.e., less than 3 times ULN). The transaminase elevations did not appear to be related to the dose of **SOMAVERT** administered, generally occurred within 4 to 12 weeks of initiation of therapy, and were not associated with any identifiable biochemical, phenotypic, or genetic predictors.

In a global post-marketing combination study with a somatostatin analogue, one out of 25 patients in the pegvisomant group and 1 out of 27 in the octreotide acetate group had transaminases greater than three or more times the upper limit of normal (ULN). Three patients out of 26 (approximately 10%) treated with the combination were found to have serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ranging from 13 to 45 times the ULN within 3 months of starting this treatment. Two of these patients received suprathreshold doses of octreotide acetate (30 mg every 2 weeks) combined with a normal dose of **SOMAVERT** (10 mg daily). All three patients completely recovered after discontinuation of treatment. The safety and efficacy of pegvisomant in combination with other medicinal products, including somatostatin analogues, in the treatment of acromegaly have not been established and, therefore, the combination of somatostatin analogues with pegvisomant is not recommended.

Baseline serum ALT, AST, TBIL, and ALP levels should be obtained prior to initiating therapy with **SOMAVERT**. **SOMAVERT** should not be initiated or continued if signs of liver disease are present, pending a comprehensive hepatic evaluation. Table 1 lists recommendations regarding initiation of treatment with **SOMAVERT**, based on the results of these liver tests (LTs).

If a patient develops LT elevations, or any other signs or symptoms of liver dysfunction while receiving **SOMAVERT**, the following patient management is recommended (Table 2).

**Table 1. Initiation of Treatment with SOMAVERT Based on Results of Liver Tests**

<b>Baseline LT Levels</b>	<b>Recommendations</b>
Normal	May treat with <b>SOMAVERT</b> . Monitor LTs at monthly intervals during the first 6 months of treatment, quarterly for the next 6 months, and then biannually for the next year.
Elevated, but less than or equal to 3 times ULN	May treat with <b>SOMAVERT</b> ; however, monitor LTs monthly for at least one year after initiation of therapy and then biannually for the next year.
Greater than 3 times ULN	Do not treat with <b>SOMAVERT</b> until a comprehensive workup establishes the cause of the patient's liver dysfunction. Determine if cholelithiasis or choledocholithiasis is present, particularly in patients with a history of prior therapy with somatostatin analogs. Based on the workup, consider initiation of therapy with <b>SOMAVERT</b> . If the decision is to treat, LTs and clinical symptoms should be monitored very closely.

**Table 2. Continuation of Treatment with SOMAVERT Based on Results of Liver Tests**

<b>LT Levels and Clinical Signs/Symptoms</b>	<b>Recommendations</b>
Elevated, but less than or equal to 3 times ULN	May continue therapy with <b>SOMAVERT</b> . However, monitor LTs monthly to determine if further increases occur.
Greater than <del>or equal to</del> 3 but less than 5 times ULN (without signs/symptoms of hepatitis or other liver injury, or increase in serum TBIL)	May continue therapy with <b>SOMAVERT</b> . However, monitor LTs weekly to determine if further increases occur (see below). In addition, perform a comprehensive hepatic workup to discern if an alternative cause of liver dysfunction is present.
At least 5 times ULN, or transaminase elevations at least 3 times ULN associated with any increase in serum TBIL (with or without signs/symptoms of hepatitis or other liver injury)	Discontinue <b>SOMAVERT</b> immediately. Perform a comprehensive hepatic workup, including serial LTs, to determine if and when serum levels return to normal. If LTs normalize (regardless of whether an alternative cause of the liver dysfunction is discovered), consider cautious reinitiation of therapy with <b>SOMAVERT</b> , with frequent LT monitoring.
Signs or symptoms suggestive of hepatitis or other liver injury (e.g., jaundice, bilirubinuria, fatigue, nausea, vomiting, right upper quadrant pain, ascites, unexplained edema, easy bruisability)	Discontinue <b>SOMAVERT</b> immediately. Immediately perform a comprehensive hepatic workup. If liver injury is confirmed, the drug should be discontinued permanently.

## **Immune**

### **Immunogenicity**

In pre-marketing clinical studies, approximately 17% of the patients had low titer, non-neutralizing anti-GH antibodies. These antibodies do not appear to have clinical significance. An assay for anti-pegvisomant antibodies in a patient receiving **SOMAVERT** is not commercially available.

### **Systemic hypersensitivity**

Systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalized skin reactions have been reported with **SOMAVERT**. Caution and close monitoring should be exercised when re-initiating **SOMAVERT** therapy (see **ADVERSE REACTIONS, Immune system disorders**).

### **Cross-Reactivity with GH Assays**

**SOMAVERT** has significant structural similarity to growth hormone (GH) which causes it to cross-react in commercially available GH assays. Since serum concentrations of therapeutically effective doses of **SOMAVERT** are generally 100 to 1000 times higher than the actual serum GH concentrations seen in patients with acromegaly, measurements of serum GH concentrations will appear falsely elevated.

## **Lipohypertrophy**

There have been cases of lipohypertrophy in patients treated with **SOMAVERT**. In a double-blind, 12-week, placebo-controlled study, there was one case (1.3%) of injection site lipohypertrophy reported in a subject receiving 10 mg/day. The subject recovered while on treatment. Among two open-label trials (with a total of 147 patients), there were two subjects, both receiving 10 mg/day, who developed lipohypertrophy. One case recovered while on treatment, and one case resulted in a discontinuation of treatment. Injection sites should be rotated daily to help prevent lipohypertrophy (different area than the last injection).

## **Special Populations**

### **Pregnant Women:**

There are no adequate and well-controlled studies in pregnant women. **SOMAVERT** should be used during pregnancy only if the potential benefit justifies the potential risk to the patient.

### **Nursing Women:**

It is not known whether pegvisomant is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **SOMAVERT** is administered to a nursing woman.

### **Pediatrics (< 18 years of age):**

The safety and effectiveness of **SOMAVERT** in pediatric patients have not been established.

### **Geriatrics (≥ 65 years of age):**

Clinical studies of **SOMAVERT** did not include sufficient numbers of subjects aged 65 and over to determine whether these subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### **Monitoring and Laboratory Tests**

#### **Liver Tests**

Recommendations for monitoring liver function are stated above (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver Tests [LTs]**).

#### **IGF-I Levels**

Treatment with **SOMAVERT** should be evaluated by monitoring serum IGF-I concentrations four to six weeks after therapy is initiated or any dose adjustments are made, and at least every six months after IGF-I levels have normalized. The goals of treatment should be to maintain a patient's serum IGF-I concentration within the age-adjusted normal range and to control the signs and symptoms of acromegaly.

#### **GH Levels**

Pegvisomant interferes with the measurement of serum GH concentrations by commercially available GH assays (see **DRUG INTERACTIONS, Drug-Laboratory Interactions**). Furthermore, even when accurately determined, GH levels usually increase during therapy with **SOMAVERT**. Therefore, treatment with **SOMAVERT** should not be monitored or adjusted based on serum GH concentrations.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Safety was evaluated in a randomized, multicenter, placebo-controlled, 12-week study, of patients treated with 10 mg/day (n=26), 15 mg/day (n=26), or 20 mg/day (n=28) of **SOMAVERT** (pegvisomant for injection) or placebo (n=32).

Table 3 shows the incidence of treatment-emergent adverse events reported in at least two patients treated with **SOMAVERT** and at frequencies greater than placebo during the 12-week, placebo-controlled study. The majority of reported adverse events were of mild to moderate intensity and limited duration. Adverse events did not appear to be dose dependent.

## 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.*

**Table 3. Number of Patients with Acromegaly (Incidence) Reporting Adverse Events in a 12-week Placebo-controlled Study with SOMAVERT<sup>1</sup>**

Event	SOMAVERT			Placebo n=32
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
<b>Body as a Whole</b>				
Infection †	6 (23%)	0	0	2 (6%)
Pain	2 (8%)	1 (4%)	4 (14%)	2 (6%)
Injection site reaction*	2 (8%)	1(4%)	3 (11%)	0
Injury	2 (8%)	1(4%)	0	1 (3%)
Back pain	2 (8%)	0	1 (4%)	1 (3%)
Influenza	1 (4%)	3 (12%)	2 (7%)	0
Chest pain	1 (4%)	2 (8%)	0	0
<b>Digestive</b>				
Liver function test Abnormal	3 (12%)	1 (4%)	1 (4%)	1 (3%)
Diarrhea	1 (4%)	0	4 (14%)	1 (3%)
Nausea	0	2 (8%)	4 (14%)	1 (3%)
<b>Nervous</b>				
Dizziness	2 (8%)	1 (4%)	1 (4%)	2 (6%)
Paresthesia	0	0	2 (7%)	2 (6%)
<b>Metabolic and nutritional disorders</b>				
Edema peripheral	2 (8%)	0	1 (4%)	0
<b>Cardiovascular</b>				
Hypertension	0	2 (8%)	0	0
<b>Respiratory</b>				
Sinusitis	2 (8%)	0	1 (4%)	1 (3%)

<sup>1</sup>Table includes only those events that were reported in at least 2 patients and at a higher incidence in patients treated with SOMAVERT than in patients treated with placebo.

† The 6 events coded as "infection" in the group treated with SOMAVERT 10 mg were reported as cold symptoms (3), upper respiratory infection (1), blister (1), and ear infection (1). The 2 events in the placebo group were reported as cold symptoms (1) and chest infection (1).

\*including injection site hypersensitivity and/or injection site hypertrophy (e.g, lipohypertrophy)

Nine acromegalic patients (5.6%) withdrew from pre-marketing clinical studies because of adverse events, including two patients with marked transaminase elevations (**WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver Tests [LTs]**), one patient with lipohypertrophy at the injection sites, and one patient with substantial weight gain.

### **Abnormal Hematologic and Clinical Chemistry Findings**

#### **Laboratory Changes**

Elevations of serum concentrations of ALT and AST greater than ten times the ULN were reported in two subjects (0.8%) exposed to SOMAVERT in pre-marketing clinical studies (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Liver Tests [LTs]**).

#### **Immunogenicity**

In pre-marketing clinical studies, approximately 17% of the patients had low titer, non-neutralizing anti-GH antibodies. These antibodies do not appear to have clinical significance. An assay for anti-pegvisomant antibodies in a patient receiving SOMAVERT is not commercially available.

### **Post-Marketing Adverse Drug Reactions**

The following adverse reactions have been identified during post-approval use of SOMAVERT. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

#### **Immune system disorders**

Systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalized skin reactions (rash, erythema, pruritus, urticaria) have been reported with SOMAVERT (see **WARNINGS AND PRECAUTIONS**). Some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients.

### **Registry of Patients with Acromegaly Treated with SOMAVERT**

ACROSTUDY is an international observational registry that captures long term safety data in patients with acromegaly treated with SOMAVERT, as used in clinical practice. Treatment dose and schedule were at the discretion of each treating physician. Although safety monitoring as per the recommended schedule was mandatory, not all assessments were performed at all time points for every patient. Because of this, comparison of rates of adverse events to those in the original clinical trial is not appropriate. In an interim report, there were 1288 patients enrolled (mean duration of treatment 3.7 years).

At the start of SOMAVERT treatment 648 patients were on SOMAVERT monotherapy for acromegaly. Of the 454 patients who had a normal AST and ALT at baseline, 4 patients had elevated tests >3 times ULN, two of whom had elevated tests >5 times ULN.

Lipohypertrophy was reported in 6 (0.5%) patients.

MRIs were compared to any previous ones, and a change in tumor volume was reported as

significant locally only if the diameter increased by more than 3 mm for microadenomas or volume increased by more than 20% for macroadenomas. All MRI changes considered significant at the local reading were reanalyzed centrally. Of the 747 patients who had a MRI reported at baseline and at least once during follow up in the study, 51 (7%) were reported to have an increase by local MRI. Of these, 16 patients (2%) had confirmation of this increase, 6 patients had a decrease, 12 had “no change”; there was 1 with insufficient data and 16 patients did not have a central MRI reading.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

Acromegalic patients with diabetes mellitus being treated with insulin and/or oral hypoglycemic agents may require dose reductions of these therapeutic agents after the initiation of therapy with **SOMAVERT** (pegvisomant for injection) (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Glucose Metabolism** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Some patients concomitantly receiving opioids required higher serum concentrations of pegvisomant to achieve appropriate IGF-I suppression as compared to patients not receiving opioids, suggesting opioids may confer a resistance to the clinical effects of pegvisomant. The mechanism of action and their clinical relevance is unclear (or unknown) (see **WARNINGS AND PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

### **Pegvisomant in combination with Somatostatin analogues**

Hepatic enzyme elevations (greater than 10 times upper limit of normal [ULN]) have been reported in patients treated with the combination of **SOMAVERT** and octreotide acetate particularly when higher than recommended doses of octreotide acetate were used. The safety and efficacy of pegvisomant in combination with other medicinal products, including somatostatin analogues, in the treatment of acromegaly have not been established and, therefore, the combination of somatostatin analogues with pegvisomant is not recommended (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

### **Drug-Laboratory Interactions**

Pegvisomant has significant structural similarity to GH, which causes it to cross-react in commercially available GH assays. Because serum concentrations of pegvisomant at therapeutically effective doses are generally 100 to 1000 times higher than endogenous serum GH levels seen in patients with acromegaly, commercially available GH assays will overestimate true GH levels. Treatment with **SOMAVERT** should therefore not be monitored or adjusted based on serum GH concentrations reported from these assays. Instead, monitoring and dose adjustments should only be based on serum IGF-I levels.

## DOSAGE AND ADMINISTRATION

### **Recommended Dose and Dosage Adjustment**

The recommended loading dose of pegvisomant is 40 mg given subcutaneously (SC), under the supervision of a healthcare provider. Proper training in SC injection technique should be provided to patients or their caregivers so that patients can receive once-daily SC injections. On the next day following the loading dose, patients or their caregivers should be instructed to begin daily injections of pegvisomant 10 mg SC.

The pegvisomant dose should be titrated to normalize serum IGF-I concentrations, and serum IGF-I concentrations should be measured every 4-6 weeks. The dose should not be based on GH concentrations. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I concentrations would benefit from increased pegvisomant dosage.

- The dose should be increased by 5 mg increments every 4-6 weeks if IGF-I concentrations are elevated.
- The dose should be decreased by 5 mg decrements every 4-6 weeks if IGF-I concentrations are below the normal range.
- IGF-I levels should also be monitored when a pegvisomant dose given in multiple injections is converted to a single daily injection.

The recommended dose range is between 10 to 30 mg SC once daily, and the maximum daily dose is 30 mg SC once daily.

Acromegalic patients with diabetes mellitus being treated with insulin and/or oral hypoglycemic agents may require dose reductions of these therapeutic agents after the initiation of therapy with **SOMAVERT** (pegvisomant for injection) (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Glucose Metabolism** and **DRUG INTERACTIONS, Drug-Drug Interactions**).

Some patients concomitantly receiving opioids may require higher serum concentrations of pegvisomant to achieve appropriate IGF-I suppression (see **WARNINGS AND PRECAUTIONS, General** and **DRUG INTERACTIONS, Drug-Drug Interactions**).

### **Administration**

**SOMAVERT** is supplied as a lyophilized powder in a vial. Each vial of **SOMAVERT** should be reconstituted with 1 mL of the diluent (Sterile Water for Injection, Ph. Eur) provided in a vial or in a pre-filled syringe that is included in the package. Detailed instructions regarding reconstitution and administration are included in the package of **SOMAVERT** and should be closely followed.

**Diluent vial presentation:**

To prepare the solution, withdraw 1 mL of Sterile Water for Injection, Ph. Eur. from the diluent vial and inject it into the vial of **SOMAVERT**, aiming the stream of liquid against the glass wall. Hold the vial between the palms of both hands and gently roll it to dissolve the powder. **DO NOT SHAKE THE VIAL**, as this may cause denaturation of pegvisomant.

**Diluent Pre-filled syringe presentation:**

To prepare the solution, inject the diluent (Sterile Water for Injection, Ph. Eur.) from the pre-filled syringe into the vial of **SOMAVERT**, aiming the stream of liquid against the glass wall. Hold the vial between the palms of both hands and gently roll it to dissolve the powder. **DO NOT SHAKE THE VIAL**, as this may cause denaturation of pegvisomant.

After reconstitution, each vial of **SOMAVERT** contains 10, 15, 20, 25 or 30 mg of pegvisomant protein in 1 mL of solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear after reconstitution. If the solution is cloudy, do not inject it. Only one dose should be administered from each vial. **SOMAVERT** should be administered within three hours after reconstitution. The site of injection should be rotated daily to help prevent lipohypertrophy.

**Reconstitution:****Parenteral Products:**

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume of diluent	Nominal Concentration per mL
8 mL	1 mL of Sterile Water for Injection, Ph. Eur	8 mL (vial) 1 mL (pre-filled syringe)	10, 15, 20, 25 or 30 mg of pegvisomant protein in 1 mL of solution

**OVERDOSAGE**

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

There was one reported incident of acute overdose with **SOMAVERT** (pegvisomant for injection) during pre-marketing clinical studies in which a patient self-administered 80 mg/day for seven days. The patient experienced a slight increase in fatigue, had no other complaints, and demonstrated no significant clinical laboratory abnormalities.

In cases of overdose, administration of **SOMAVERT** should be discontinued and not resumed until IGF-I levels return to within or above the normal range.

## ACTION AND CLINICAL PHARMACOLOGY

### Pharmacodynamics

**SOMAVERT** (pegvisomant for injection) contains pegvisomant for injection, an analog of human growth hormone (GH) that has been structurally altered to act as a GH receptor antagonist.

Pegvisomant selectively binds to GH receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with GH signal transduction. Pegvisomant is highly selective for the GH receptor, and does not cross-react with other cytokine receptors, including prolactin. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGFBP-3 (IGF binding protein-3), and the acid-labile subunit (ALS).

### Pharmacokinetics

**Absorption:** Following subcutaneous administration, peak serum pegvisomant concentrations are not generally attained until 33 to 77 hours after administration. The mean extent of absorption of a 20-mg subcutaneous dose was 57%, relative to a 10-mg intravenous dose.

**Distribution:** The mean apparent volume of distribution of pegvisomant is 7 L (12% coefficient of variation), suggesting that pegvisomant does not distribute extensively into tissues. Proportional increases in  $C_{max}$  and AUC are not observed when pegvisomant is given in single, escalating doses; however, approximate dose linear pharmacokinetics are observed at steady state following multiple doses. Mean  $\pm$  SD serum pegvisomant concentrations after long term therapy with daily doses of 10, 15, and 20 mg were  $9300 \pm 6300$ ;  $14,300 \pm 7500$ ; and  $18,100 \pm 10,100$  ng/mL, respectively.

Studies in rats show that radiolabeled pegvisomant does not cross the blood-brain barrier.

**Metabolism and Excretion:** The pegvisomant molecule contains covalently bound polyethylene glycol polymers in order to reduce the clearance rate. The mean total body systemic clearance of pegvisomant following multiple doses is estimated to be 28 mL/h (95% CI: 23.8, 32.4 mL/h) for subcutaneous doses ranging from 10 to 20 mg/day. Clearance of pegvisomant was found to increase by 0.6 mL/h for each kilogram of body weight above 94 kg. Pegvisomant had a mean serum half-life of  $138 \pm 68$  hours following a 20 mg subcutaneous dose. Less than 1% of administered drug is recovered in the urine over 96 hours, suggesting that renal excretion is not the primary route of elimination. The elimination route of pegvisomant has not been studied in humans.

The relative bioavailability of 1 x 30 mg pegvisomant was compared to 2 x 15 mg pegvisomant in a single dose study. The AUC<sub>inf</sub> and C<sub>max</sub> of pegvisomant when administered as one injection of 30 mg strength was approximately 6% and 4% greater, respectively, as compared to when administered as two injections of 15 mg strengths.

### Special Populations and Conditions

**Pediatrics:** Differences in the pharmacokinetics of **SOMAVERT** in these populations has not been studied.

**Geriatrics:** Differences in the pharmacokinetics of **SOMAVERT** in these populations has not been studied.

**Gender:** No gender effect on the pharmacokinetics of **SOMAVERT** was found in a population pharmacokinetic analysis.

**Race:** Differences in the pharmacokinetics of **SOMAVERT** in these populations has not been studied.

**Hepatic/Renal Insufficiency:** No pharmacokinetic studies have been conducted in patients with renal insufficiency or hepatic insufficiency.

## **STORAGE AND STABILITY**

- The 30 day packages contain 30 diluent pre-filled syringes and 30 vials of SOMAVERT powder (The 30 vials are supplied within 3 smaller boxes (10 vials per small box)).
- The 1 day package contain either:
  - One pre-filled syringe and one vial of SOMAVERT powder.
  - or
  - One diluent vial and one vial of SOMAVERT powder

Prior to reconstitution, **SOMAVERT** (pegvisomant for injection) should be stored as follows:

- 30 day packages
  - 30 Pre-filled syringes:
    - If room temperature is below 30°C, the pre-filled syringes may be stored at room temperature (below 30°C);
    - If room temperature is above 30°C, the pre-filled syringes should be stored in a refrigerator (2°C - 8°C). Protect from freezing.
- 30 Vials
  - Store all 3 boxes of vials of SOMAVERT powder in a refrigerator (at 2 to 8 °C). Protect the vials from light. Protect from freezing.
- One day packages
  - Store the entire package in the refrigerator (at 2 to 8°C). Protect from freezing. Protect the vials from light.
  - Pre-filled syringe:

- If room temperature is below 30°C, only the diluent pre-filled syringe may be stored at room temperature (below 30°C).
- If room temperature is above 30°C, the diluent pre-filled syringe should be stored in a refrigerator (2°C - 8°C). Protect from freezing.

### **Reconstituted Solutions**

**SOMAVERT** should be administered within three hours of reconstitution. Only one dose should be administered from each vial.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Availability of Dosage Forms**

**SOMAVERT** (pegvisomant for injection) is available in single-dose vial in the following 5 strengths, in packages that also include vials with 8 mL of Sterile Water for Injection, Ph. Eur. or with pre-filled syringes with 1 mL of Sterile Water for Injection, Ph. Eur. Pack size of 1 or 30.

**SOMAVERT** 10 mg, 15 mg, 20 mg, 25 mg, 30 mg are all available in the following presentations:

- Package of 1 vial of **SOMAVERT** powder with 1 diluent pre-filled syringe
- Packages of 30 vials of **SOMAVERT** powder with 30 diluent pre-filled syringes
- Package of 1 vial of **SOMAVERT** powder with diluent vial

The stoppers on the vial of **SOMAVERT** and the vial of diluent are latex free.

### **Composition**

**SOMAVERT** is supplied as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of Sterile Water for Injection, Ph. Eur. It is available in single-dose vials containing 10, 15, 20, 25 and 30 mg of pegvisomant protein. The diluent (Sterile Water for Injection, Ph. Eur) is provided in a vial or in a pre-filled syringe that is included in the same package as the **SOMAVERT** vial. Each 10, 15 and 20 mg vial also contains 1.36 mg of glycine, 36.0 mg of mannitol, 1.04 mg of sodium phosphate dibasic anhydrous, and 0.36 mg of sodium dihydrogen phosphate, monohydrate. Each 25 mg vial also contains 1.7 mg of glycine, 45.0 mg of mannitol, 1.3 mg of sodium phosphate dibasic anhydrous, and 0.45 mg of sodium dihydrogen phosphate monohydrate. Each 30 mg vial also contains 2.04 mg of glycine, 54.0 mg of mannitol, 1.56 mg of sodium phosphate dibasic anhydrous, and 0.54 mg of sodium dihydrogen phosphate monohydrate.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Pegvisomant for Injection

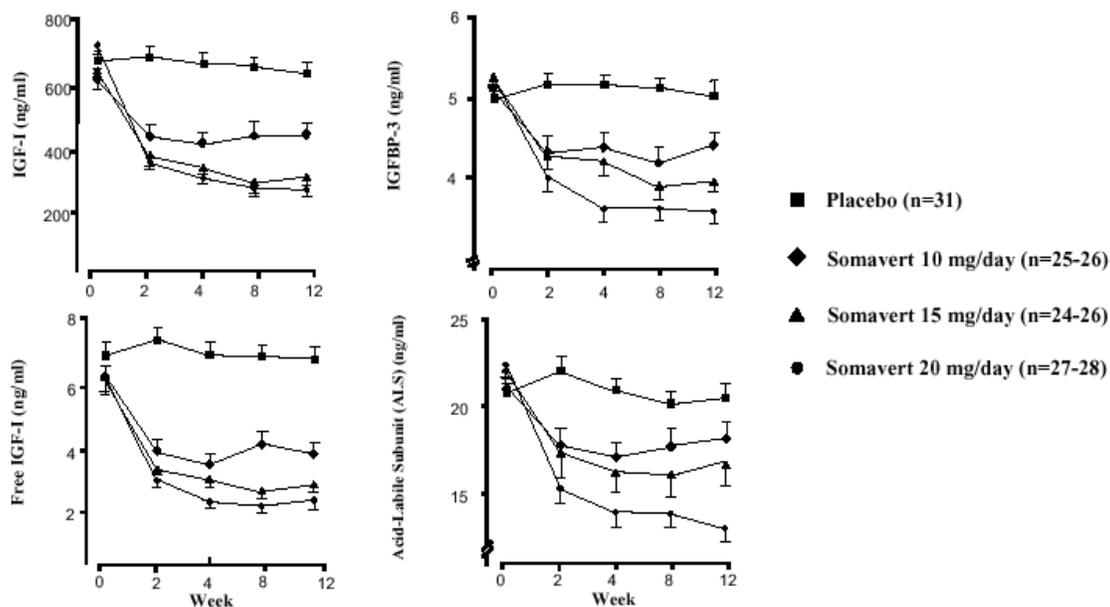
Molecular formula:  $C_{980}H_{1519}N_{259}O_{303}S_7 \bullet [(CH_2CH_2O)_{112 \pm 10\%} - CH_2CH_2O]_{4-6}$

Description: Pegvisomant is a protein containing 191 amino acid residues, to which polyethylene glycol (PEG) polymers are covalently bound (predominantly 4 to 6 PEG/protein molecule). The average molecular weight of the PEG polymers is 5000 daltons. The amino acid sequence of the pegvisomant protein is the same as that for human GH, except for substitutions at nine residues. Pegvisomant is synthesized in a special strain of *Escherichia coli* bacteria that has been genetically modified by the addition of a plasmid that carries a gene for GH receptor antagonist.

#### CLINICAL TRIALS

One hundred twelve patients with acromegaly previously treated with surgery, radiation therapy, and/or medical therapies participated in a 12-week, randomized, double-blind, multi-center study comparing placebo and **SOMAVERT** (pegvisomant for injection). Following withdrawal from previous medical therapy, the 80 patients randomized to treatment with **SOMAVERT** received an 80 mg subcutaneous (SC) loading dose, followed by fixed doses of 10, 15, or 20 mg/day SC. The three groups that received **SOMAVERT** showed dose-dependent, statistically significant reductions in serum levels of IGF-I, free IGF-I, IGFBP-3, and ALS compared with placebo at all post-baseline visits (Figure 1 and Table 4).

**Figure 1. Effects of SOMAVERT on Serum Markers (Mean ± Standard Error)**



**Table 4. Mean Change (95% Confidence Interval) in Serum Markers at Week 12**

	SOMAVERT			Placebo n=31
	10 mg/day n=25-26	15 mg/day n=24-26	20 mg/day n=27-28	
Mean percent change in IGF-I	-26.7* (-38.0, -15.5)	-48.3* (-58.9, -37.6)	-62.5* (-70.7, -54.2)	-4.0 (-10.1, 2.2)
Mean change in free IGF-I (ng/mL)	-2.5 <sup>†</sup> (-3.7, -1.4)	-3.6 <sup>‡</sup> (-5.1, -2.2)	-3.9 <sup>‡</sup> (-5.4, -2.5)	-0.2 (-1.2, 0.9)
Mean change in IGFBP-3 (ng/mL)	-0.7 <sup>†</sup> (-1.1, -0.3)	-1.6 <sup>‡</sup> (-2.2, -1.0)	-1.6 <sup>‡</sup> (-2.0, -1.2)	-0.1 (-0.4, 0.2)
Mean change in ALS (ng/mL)	-3.1 <sup>†</sup> (-4.7, -1.5)	-6.4 <sup>‡</sup> (-8.7, -4.0)	-9.5 <sup>‡</sup> (-11.2, -7.8)	-0.5 (-1.8, 0.9)

\* p value versus placebo ≤ 0.0001

† p value versus placebo < 0.05

‡ p value versus placebo < 0.001

After 12 weeks of treatment, serum IGF-I levels were normalized in 10% (95% CI: 0.2, 0.1), 39% (95% CI: 19.8, 57.2), 75% (95% CI: 57.7, 92.3), and 82% (95% CI: 68.0, 96.3) of subjects treated with placebo, 10, 15, or 20 mg/day of **SOMAVERT**, respectively (Figure 2).

**Figure 2. Percent of Patients Whose IGF-I Levels Normalized at Week 12**

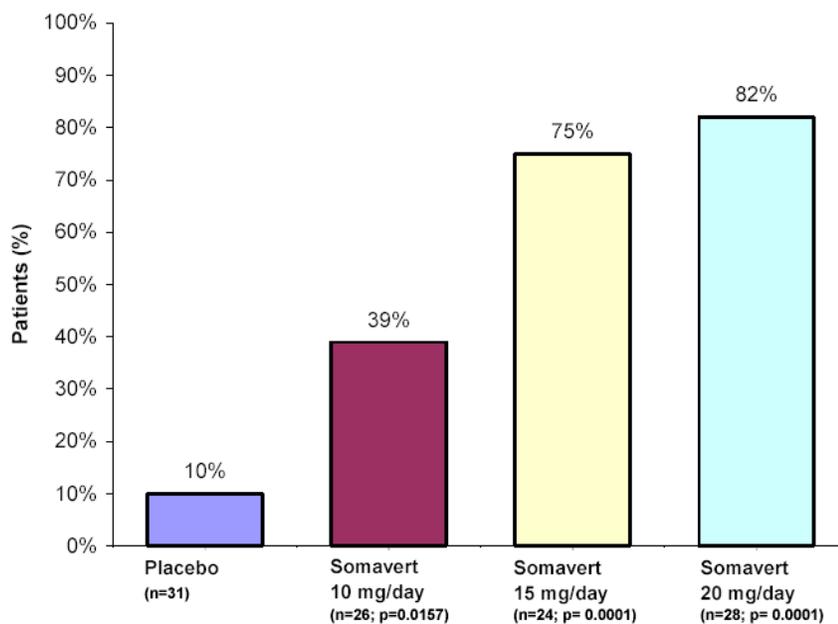


Table 5 shows the effect of treatment with **SOMAVERT** on ring size and on signs and symptoms of acromegaly. Ring size at week 12 was significantly smaller (improved) in the groups treated with 15 or 20 mg of **SOMAVERT**, compared with placebo. The total score for signs and symptoms at week 12 was significantly lower (improved) in each of the groups treated with **SOMAVERT**, compared with the group treated with placebo.

**Table 5. Mean Change from Baseline (95% Confidence Interval) at Week 12 for Ring Size and Signs and Symptoms of Acromegaly**

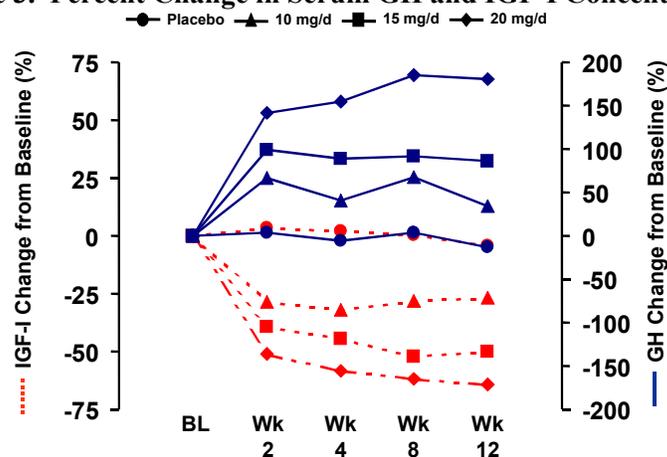
	SOMAVERT			Placebo n=30
	10 mg/day n=26	15 mg/day n=24-25	20 mg/day n=26-27	
<b>Ring size</b>	-0.8 (-1.5, -0.2)	-1.9 <sup>†</sup> (-2.8, -1.1)	-2.5 <sup>†</sup> (-3.8, -1.2)	-0.1 (-1.0, 0.7)
<b>Total score for signs and symptoms of acromegaly</b>	-2.5* (-4.2, -0.8)	-4.4* (-6.9, -1.9)	-4.7 <sup>†</sup> (-6.6, -2.9)	1.3 (-0.9, 3.6)
<b>Soft-tissue swelling</b>	-0.7 (-1.4, -0.1)	-1.2* (-2.2, -0.3)	-1.3 <sup>†</sup> (-1.8, -0.8)	0.3 (-0.5, 1.1)
<b>Arthralgia</b>	-0.3 (-1.0, 0.4)	-0.5 (-1.5, 0.5)	-0.4 (-1.2, 0.4)	0.1 (-0.6, 0.7)
<b>Headache</b>	-0.4 (-1.0, 0.2)	-0.3 (-0.9, 0.4)	-0.3 (-1.1, 0.5)	0.1 (-0.5, 0.7)
<b>Perspiration</b>	-0.6 (-1.3, 0.02)	-1.1* (-1.7, -0.6)	-1.7 <sup>†</sup> (-2.3, -1.1)	0.1 (-0.5, 0.8)
<b>Fatigue</b>	-0.5* (-1.0, 0.1)	-1.3 <sup>†</sup> (-2.0, -0.6)	-1.0* (-1.7, -0.4)	0.7 (0.2, 1.3)

\* p value versus placebo ≤ 0.05

† p value versus placebo ≤ 0.001

Serum GH concentrations, as measured by research assays using antibodies that do not cross-react with pegvisomant (see **DRUG INTERACTIONS, Drug-Laboratory Interactions**), rise within two weeks of beginning treatment with **SOMAVERT**. The largest GH response was seen in patients treated with doses of **SOMAVERT** greater than 20 mg/day. This effect is presumably the result of diminished inhibition of GH secretion as IGF-I levels fall. As shown in Figure 3, when patients with acromegaly were given an 80 mg loading dose of **SOMAVERT** followed by a fixed daily dose, this rise in GH was inversely proportional to the fall in IGF-I and generally stabilized by week 2. Serum GH concentrations also remained stable in patients treated with **SOMAVERT** for up to 18 months. Increases of serum GH concentrations were not associated with pituitary tumor enlargement (see **WARNINGS AND PRECAUTIONS, Tumor Growth**).

**Figure 3. Percent Change in Serum GH and IGF-I Concentrations**



Another cohort of 38 patients with acromegaly was treated with **SOMAVERT** in a long-term, open-label, dose-titration study and received at least 12 consecutive months of daily dosing with **SOMAVERT** (mean = 85 weeks). The mean ( $\pm$  SD) IGF-I concentration at baseline in this cohort was 917 ( $\pm$  356) ng/mL after withdrawal from previous medical therapy, falling to 303 ( $\pm$  163) ng/mL at the end of treatment with **SOMAVERT**. Thirty-six of the 38 patients (94.7%) achieved a normal (age-adjusted) IGF-I concentration. After the first visit at which a normal IGF-I concentration was observed, IGF-I levels remained within the normal range at 92% of all subsequent visits over a mean duration of one year.

In a separate long-term, open-label, dose titration study, 108 patients with acromegaly received **SOMAVERT** for a mean duration of 43 weeks. The mean ( $\pm$  SD) IGF-I concentration at baseline in this cohort was 718 ( $\pm$  324) ng/mL after withdrawal from previous medical therapy, falling to 381 ( $\pm$  200) ng/mL at the end of treatment with **SOMAVERT**. One hundred of the 108 patients (92.6%) achieved a normal (age-adjusted) IGF-I concentration.

A subgroup analysis of the data from the 12-week study demonstrated that **SOMAVERT** was effective in those patients whose IGF-1 level was not adequately controlled on somatostatin analog therapy. In those patients classified as resistant to somatostatin analogs (n=30), the percentage of patients who achieved a normal (age-adjusted) IGF-I concentration after 12 weeks was 61.9%. When allowed to titrate the **SOMAVERT** dose based on IGF-1 levels during the long-term, open-label, dose titration study, 93.3% of patients in this somatostatin analog resistant group were documented with a normal IGF-I concentration. Similarly, 78.6% of patients classified as responsive to somatostatin analogs (n=19) achieved a normal IGF-1 concentration after 12 weeks on **SOMAVERT**; this increased to 89.5% in the long-term, open-label, dose-titration study.

## TOXICOLOGY

The toxicity of pegvisomant was evaluated in studies of up to six months, in mice, rats and monkeys.

### Acute Toxicity

Administration of pegvisomant to mice as a single dose of up to 10 mg/kg either intravenously (IV) or subcutaneously (SC) or to cynomolgus monkeys as single IV doses of 15 or 100 mg/kg did not result in any treatment-related toxic findings.

### Long-term Toxicity

The repeated dose toxicity of pegvisomant was characterized in 2 week studies in mice, a 4 week study in rhesus monkeys and 26 week studies in rats and rhesus monkeys.

IV administration of pegvisomant for 2 weeks to mice caused local irritation at the injection site at doses  $\geq 1$  mg/kg/day. Body weight gain was reduced in males at 3 mg/kg/day. Additional findings included increases in serum total protein, albumin and phosphorus, and decreases in serum glucose, chloride, and alkaline phosphatase. Liver changes, characterized by areas of increased hepatocellular basophilia and decreased hepatocellular pallor, were observed at doses of 1 and 3 mg/kg/day and were considered to be physiological rather than toxicological in nature.

SC administration of pegvisomant for 2 weeks to mice resulted in elevated serum total protein, albumin, calcium, cholesterol, and albumin/globulin ratios as well as decreased serum glucose, potassium, chloride, and alkaline phosphatase. Livers of mice administered  $\geq 1$  mg/kg/day had areas of increased hepatocellular basophilia and decreased hepatocellular pallor. These findings were considered to be physiological responses to the treatment rather than toxicological.

Administration of pegvisomant to the rhesus monkey every other day for 4 weeks was associated with slight swelling and minimal to slight hemorrhage at injection sites in a small number of animals. Body weight gain was reduced in males at doses  $\geq 1$  mg/kg/day and in females at all dose levels. Females at 3 mg/kg/day had slightly decreased hemoglobin concentrations, packed cell volumes and red blood cell counts. Serum alkaline phosphatase was decreased in both males and females at doses  $\geq 1$  mg/kg/day. Microscopic examination of the tissues revealed no evidence of systemic toxicity.

Daily SC administration of pegvisomant for 26 weeks in rats caused decreases in body weight and food consumption in males at 30 mg/kg/day. Serum alkaline phosphatase was decreased in males at all dose levels and in females at 30 mg/kg/day. Additional findings in females were increases in kidney weights at 30 mg/kg/day, and increases in urine protein and leukocytes and increased incidences of nephropathy at doses of 3 mg/kg/day and above. Liver weights were increased in females at doses  $\geq 10$  mg/kg/day. Microscopically, hepatocellular vacuolation was seen in both sexes at 30 mg/kg/day. Localized effects at the injection sites included thickening of the skin, microscopically observed inflammation and submandibular lymph node macophage vacuolation at all dose levels. All of these effects, when present, were reversible for animals from the 3 mg/kg/day group.

Weekly SC administration of pegvisomant to the rhesus monkey for 26 weeks resulted in changes associated with the pharmacological activity of the compound such as fatty infiltration of some tissues, mild anemia, lowered white cell counts and reduction in bone and bone marrow. These changes were accompanied by reduced serum phosphorus, alkaline phosphatase and IGF-I concentrations. With the exception of the reduction in serum phosphorus and bone marrow, all of these changes were reversible or trended towards normal during an 8-week recovery period. The no-observed-adverse-effect level (NOAEL) was 1 mg/kg/day.

### **Carcinogenicity**

Pegvisomant demonstrated an anti-tumor effect, when given SC to mice bearing human meningioma tumors, four lines of human breast tumors or murine colon tumors. In most cases, pegvisomant administration significantly reduced tumor growth or the number of metastases. The mechanism of the anti-tumor activity is suggested to be through the GH/IGF-I axis. Pegvisomant reduces tumor growth through reduction in the tumor mitogen IGF-I. Since its sole mechanism of action is on GH receptors, pegvisomant is not likely to have tumor initiation or tumor promoting ability and hence has no potential to act as a carcinogen.

A two year carcinogenicity study was performed in male and female rats at subcutaneous doses up to 20 mg/kg/day (approximately 12 times the anticipated clinical exposure at 30 mg/day based on body surface area). Malignant fibrous histiocytomas were found at injection sites in male rats only, but not in female rats, and only at the mid and high doses. The incidence of these tumors was dose dependent and correlated with a dose dependent increase in irritation and inflammation at the injection sites. This response is consistent with literature reports of inert, nongenotoxic biomaterials producing this type of neoplasm in rodents after chronic subcutaneous injection.

### **Mutagenicity**

Pegvisomant was not mutagenic in the Ames test or clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes.

### **Reproduction and Teratology**

Early embryonic development and teratology studies were conducted in rabbits with pegvisomant administered SC at doses of 1, 3, and 10 mg/kg/day. No teratogenic potential was revealed, but there was an increase in implantation loss at the dose of 10 mg/kg/day. This finding may have been due to decreased IGF-I concentrations and/or GH activity, below normal, in maternal animals as opposed to the expected clinical situation where IGF-I levels will be normalized. No reproductive toxicity studies were conducted in rats because pegvisomant is not pharmacologically active in rodents.

### **Other Studies**

Pegvisomant was administered to rabbits as SC injections of 3 mg/kg on Days 0, 1, 2, 6, 7 and 8 of the study. Histopathological examination revealed minimal infiltration at all injection sites. These changes were considered to be due to the route of administration but not due to dermal irritation.

### **REFERENCES**

1. Ross RJM, Leung KC, Maamra M, et al. Binding and functional studies with the growth hormone receptor antagonist, B2036-PEG (Pegvisomant), reveal effects of pegylation and evidence that it binds to a receptor dimer. *J Clin Endocrinol Metab* 2001;86:1716-23.
2. Trainer PJ, Drake WM, Katznelson L, et al. Treatment of acromegaly with the growth hormone-receptor agonist pegvisomant. *N Engl J Med* 2000;342:1171-7.
3. van der Lely AJ, Hutson RK, Trainer PJ, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001;358:1754-9.
4. Anonymous. Integumentary System. In: Greaves P, editor. *Histopathology of Preclinical Toxicity Studies, Interpretation and Relevance in Drug Safety Evaluation*. 3rd ed. Amsterdam: Elsevier 2007: p. 10-67.
5. Greaves P. Soft tissue tumors including cardiovascular lesions. In: Bannasch P, Gossner W, editors. *Pathology of Neoplasia and Preneoplasia in Rodents*. 2nd ed. Stuttgart: Schattauer; 1997: p. 183-201.
6. Greaves P, Barsoum N. Tumors of soft tissues. In: Turusov V, Mohr U, editors. *Pathology of Tumours in Laboratory Animals, Tumours of the Rat*. Lyon: IARC Scientific Publications 1990: p. 597-613.

## PART III: CONSUMER INFORMATION

### PrSOMAVERT\* pegvisomant for injection

SOMAVERT single-dose vial with pre-filled syringe diluent  
**This leaflet is part III of a three-part "Product Monograph" published when SOMAVERT (pegvisomant for injection) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SOMAVERT. Contact your doctor or pharmacist if you have any questions about the drug.**

#### ABOUT THIS MEDICATION

Your doctor has prescribed SOMAVERT (pegvisomant for injection) for you. Read these instructions completely before using SOMAVERT and each time you renew your prescription, just in case anything has changed. If there is anything you do not understand or cannot do, contact your healthcare professional. These instructions do not take the place of careful discussions with your doctor.

#### What the medication is used for:

SOMAVERT is a medicine used to treat acromegaly, which is a disease caused when the body produces too much growth hormone.

#### What it does:

SOMAVERT blocks the effect of too much growth hormone and improves the symptoms of acromegaly.

#### When it should not be used:

You should not use this medicine if you have had an allergic reaction to SOMAVERT or any of its ingredients. The stopper on the vial of SOMAVERT is latex free.

#### What the medicinal ingredient is:

The active ingredient is pegvisomant.

#### What the important nonmedicinal ingredients are:

None. The inactive ingredients are glycine, mannitol, sodium phosphate dibasic anhydrous, and sodium dihydrogen phosphate monohydrate.

#### What dosage forms it comes in:

SOMAVERT is supplied as a sterile powder intended for subcutaneous (under the skin) injection after reconstitution with 1 mL of Sterile Water for Injection (Ph. Eur.). It is available in single-dose vials containing 10, 15, 20, 25 or 30 mg of pegvisomant protein. The diluent (Sterile Water for Injection, Ph. Eur) is provided in a pre-filled syringe that is included in the same package as the SOMAVERT vial.

#### WARNINGS AND PRECAUTIONS

**BEFORE you use SOMAVERT talk to your doctor or pharmacist if you:**

- Have liver disease now, or have had liver disease in the past.
- Take insulin or anti-diabetes drugs, because the dose of these medicines may need to be changed when you use SOMAVERT.
- Take narcotic painkillers (opioid medicines), because the dose of SOMAVERT may need to be changed when you take these medicines.
- Plan to become pregnant, or if you are pregnant, might be pregnant, or do not use effective birth control.
- Plan to breast-feed, or if you are already breast-feeding.

#### INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medications (prescription and non-prescription) you are using. It is especially important that your doctor know if you are taking insulin or anti-diabetes drugs and opioids.

Combination treatment involving SOMAVERT and somatostatin analogues (drugs used to treat acromegaly) may increase risk of liver problems.

#### PROPER USE OF THIS MEDICATION

SOMAVERT is intended for subcutaneous (under the skin) administration. Your first dose, called a loading dose, will be given to you by a health care professional. Following this, your health care professional will instruct you to inject SOMAVERT subcutaneously once a day. You and any caregiver who may give you the injections should receive individual training under the supervision of the prescribing doctor.

Always follow the detailed instructions that are given below (INSTRUCTIONS FOR USE) when you are preparing or injecting SOMAVERT. However, these instructions do not replace the individual training by a health care professional.

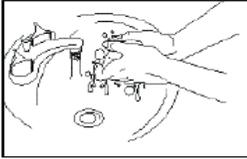
#### INSTRUCTION FOR USE

SOMAVERT is packaged in dry powdered form. Before you use SOMAVERT, it must first be reconstituted. This means it is mixed with a liquid called a diluent. The diluent is in the same packaging with the medicine. It is called Sterile Water for Injection, Ph. Eur. It is the only approved diluent for reconstituting SOMAVERT. Do not use any other liquid to reconstitute the medicine.

Use only one dose from each vial (small bottle) of SOMAVERT.

### Getting Started

Remove one package of **SOMAVERT** from the refrigerator and allow it to warm up to room temperature for approximately 10 minutes while you get ready to prepare your injection.

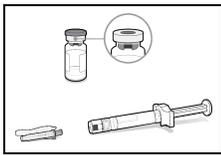


1. Wash your hands with soap and warm water. Dry your hands well.

Peel open the packaging of the syringe and safety needle to make it easier to pick up each item as you prepare for your injection.

Do not use the syringe or vial if:

- they are damaged or faulty;
- the expiration date has passed;
- it has been frozen, even if it has now thawed (syringe only).



2. Gather the necessary supplies:
  - The package of **SOMAVERT** that is now at room temperature, contains one vial of powder (**SOMAVERT**), one pre-filled syringe of liquid (Sterile Water for Injection, Ph. Eur.) and a safety needle

You will also need:

- Alcohol or antiseptic swabs
- Proper container for throwing away used needles.

### Reconstituting SOMAVERT



3. Remove the cap from the top of the vial. Take care not to touch the rubber vial stopper. At this point, the stopper is clean. If the stopper is touched by anything, you must clean it with an antiseptic or alcohol swab before use.



4. Snap off the syringe cap. It may take more effort to snap off than you might expect. Throw the syringe cap away; it is not needed again. Keep the syringe upright to avoid leakage.

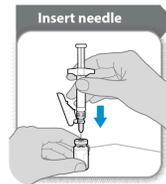
**Caution:** Do not let the end of the syringe touch anything when the syringe cap is off.



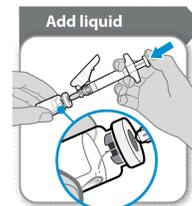
5. Twist the safety needle firmly onto the syringe as far as it will go.



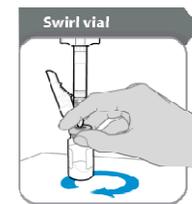
6. Fold the needle guard out of the way of the needle cover. Carefully pull the needle cover straight off. Throw the needle cover away; it is not needed again. **Caution:** Do not let the needle touch anything.



7. Push the needle through the center of vial stopper, as shown. Support the syringe while the needle is in the vial stopper to prevent bending the needle.



8. Tilt both the vial and syringe at an angle, as shown. Push the plunger rod down slowly until all the liquid has emptied into the vial. **Caution:** Do not squirt the liquid directly onto the powder, as this creates foam. Foam makes the medicine unusable. **Do not withdraw the needle yet.**

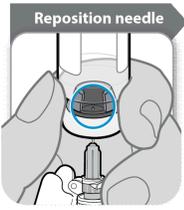


9. Support both the syringe and vial in one hand, as shown. Gently swirl the liquid, sliding the vial in a circular motion on a flat surface. Continue swirling the liquid until all the powder has fully dissolved. **Note:** This may take up to 5 minutes.



10. Keeping the needle in the vial, look carefully at the medicine. It must be clear and free of particles. Do not use if:

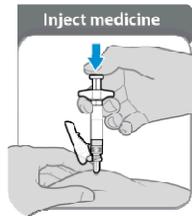
- the medicine is cloudy or hazy;
- the medicine has any colour at all;
- there are any particles or there is a layer of foam in the vial.



11. Turn the vial so that you can see the stopper gap, as shown.

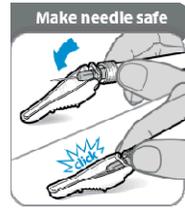
Pull the needle down so that the needle tip is at the lowest point in the liquid. This will help you to draw off as much liquid as possible.

Check that the plunger rod has not moved—if it has, then push it back all the way into the syringe. This ensures that all air is removed from the syringe before you draw off the dose.



15. Be sure to keep the needle all the way into the skin while you slowly push the syringe plunger in until the barrel is empty.

Release the pinched skin. Wait 3 to 5 seconds and then pull the needle straight out.



16. Fold the needle guard over the needle. **Gently** apply pressure using a hard surface to lock the needle guard in place. **Note:** You will hear a click when the needle guard has been locked.



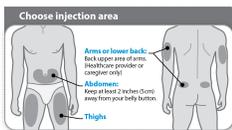
12. Slowly pull back the plunger rod to withdraw as much medicine as possible from the vial. **Note:** If you see air in the syringe, tap the barrel to float the bubbles to the top and then gently push the bubbles out into the vial. Pull the needle out of the vial.



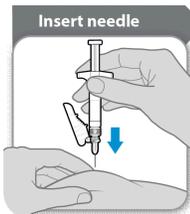
17. Do not rub the injection area. A small amount of bleeding may occur. If necessary, apply a clean, dry cotton swab over the area and press gently for 1 or 2 minutes, or until the bleeding has stopped.

### Giving the Injection

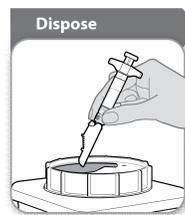
Subcutaneous (under the skin) injection sites may include the upper arm, lower back, upper thigh, abdomen (stomach area) and buttocks. Select the injection site from one of the areas identified by your health care professional. Select a different injection site each day so lumps do not develop. It may be helpful to keep a record of each day's injection site as you take your daily dose of **SOMAVERT**. Do not use an area that has a rash or broken skin, or is bruised or lumpy.



13. Prepare the injection site area as instructed by your health care professional. If you clean the site with an antiseptic or alcohol, let the skin dry before injecting the medicine.



14. With one hand, gently pinch up the skin at the site of injection. Hold the syringe with the other hand. In a single, smooth motion, push the needle completely into the skin straight down, at a 90-degree angle.



18. The syringe and needle should NEVER be reused. Safely throw away needles as directed by your health care professional, according to local environmental health regulations.

Your health care professional or pharmacist can give you information about throwing away the needles correctly. Be certain to store and throw away your treatment materials in a way that reduces danger to others.

### Overdose:

In cases of overdose, administration of **SOMAVERT** should be discontinued and not resumed. If you have taken more **SOMAVERT** than you should, contact your doctor or a poison control centre immediately.

### Missed Dose:

If you forget to give yourself an injection of **SOMAVERT**, get back on the schedule the next day. Do not inject a double dose to make up for a forgotten injection.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

**SOMAVERT** is generally well tolerated. The side effects are usually mild and do not last long. The following is not a complete list of side effects. Ask your doctor to tell you about the other side effects.

The most common side effects related to the use of the drug are pain, infection, reaction at the site of injection, influenza, and nausea.

Mild to serious allergic (anaphylactic) reactions have been reported in some patients taking **SOMAVERT**. Symptoms of a serious allergic reaction may include one or more of the following: swelling of the face, tongue, lips, or throat; wheezing or trouble breathing (spasm of the larynx); generalized skin rash, nettle rash (urticaria) or itching; or dizziness. Contact your doctor immediately if you develop any of these symptoms.

Caution and close monitoring by your doctor should be exercised when re-initiating **SOMAVERT** therapy.

A small number of patients who have used **SOMAVERT** have developed liver problems. Immediately stop therapy with **SOMAVERT** and contact your doctor if you notice any of the following:

- Sudden yellowing of the skin or whites of the eyes, or darkening of the urine
- Unexplained fatigue, nausea, vomiting, or pain in the abdomen (stomach area).

Your doctor will draw some of your blood before and during treatment with **SOMAVERT** to check how you are responding to the medicine, to change the dose if necessary, and to check for potential liver problems.

Some patients may develop changes in their blood sugar level. Your doctor may change your dose of diabetes medicine while you take **SOMAVERT**.

Some patients may develop skin thickening at the injection site that could lead to lumps (lipohypertrophy).

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

## HOW TO STORE IT

Until you mix the powder and the liquid, store the package of **SOMAVERT** as follows:

- 30 day packages
  - If room temperature is below 30°C, the pre-filled syringes may be stored at room temperature (below 30°C);
  - If room temperature is above 30°C, the pre-filled syringes should be stored in a refrigerator (2°C - 8°C). Protect from freezing.
- 30 Vials:
  - Store all 3 boxes of vials of **SOMAVERT** powder in a refrigerator (at 2 to 8 °C). Protect the vials from light. Protect from freezing.
- One day packages
  - Store the entire package in the refrigerator (at 2 to 8°C). Protect from freezing. Protect the vials from light.
  - Pre-filled syringe:
    - If room temperature is below 30°C, only the diluent pre-filled syringe may be stored at room temperature (below 30°C).
    - If room temperature is above 30°C, the diluent pre-filled syringe should be stored in a refrigerator (2°C - 8°C). Protect from freezing.

After reconstitution (mixing the powder and liquid), you may keep the mixed medicine at room temperature inside the syringe, but you must inject the mixed **SOMAVERT** within 3 hours. If you have not used the mixed medicine within 3 hours, throw it away.

**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:

By toll-free telephone: 1-866-234-2345

By toll-free fax: 1-866-678-6789

Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:  
Canada Vigilance Program  
Health Canada  
Postal Locator 1908C  
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](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. 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 at:

<http://www.pfizer.ca>

or by calling 1-800-463-6001

This leaflet was prepared by Pfizer Canada ULC

Last revised: 15 May 2019

## PART III: CONSUMER INFORMATION

### PrSOMAVERT\* pegvisomant for injection

SOMAVERT single-dose vial with diluent vial

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

#### ABOUT THIS MEDICATION

Your doctor has prescribed SOMAVERT (pegvisomant for injection) for you. Read these instructions completely before using SOMAVERT and each time you renew your prescription, just in case anything has changed. If there is anything you do not understand or cannot do, contact your healthcare professional. These instructions do not take the place of careful discussions with your doctor.

#### What the medication is used for:

SOMAVERT is a medicine used to treat acromegaly, which is a disease caused when the body produces too much growth hormone.

#### What it does:

SOMAVERT blocks the effect of too much growth hormone and improves the symptoms of acromegaly.

#### When it should not be used:

You should not use this medicine if you have had an allergic reaction to SOMAVERT or any of its ingredients. The stoppers on the vial of SOMAVERT and the vial of diluent are latex free.

#### What the medicinal ingredient is:

The active ingredient is pegvisomant.

#### What the important nonmedicinal ingredients are:

None. The inactive ingredients are glycine, mannitol, sodium phosphate dibasic anhydrous, and sodium dihydrogen phosphate monohydrate.

#### What dosage forms it comes in:

SOMAVERT is supplied as a sterile powder intended for subcutaneous (under the skin) injection after reconstitution with 1 mL of Sterile Water for Injection (Ph. Eur.). It is available in single-dose vials containing 10, 15, 20, 25 or 30 mg of pegvisomant protein. The diluent (Sterile Water for Injection, Ph. Eur) is provided in a vial that is included in the same package as the SOMAVERT vial.

#### WARNINGS AND PRECAUTIONS

**BEFORE you use SOMAVERT talk to your doctor or pharmacist if you:**

- Have liver disease now, or have had liver disease in the past.
- Take insulin or anti-diabetes drugs, because the dose of these medicines may need to be changed when you use SOMAVERT.
- Take narcotic painkillers (opioid medicines), because the dose of SOMAVERT may need to be changed when you take these medicines.
- Plan to become pregnant, or if you are pregnant, might be pregnant, or do not use effective birth control.
- Plan to breast-feed, or if you are already breast-feeding.

#### INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medications (prescription and non-prescription) you are using. It is especially important that your doctor know if you are taking insulin or anti-diabetes drugs and opioids.

Combination treatment involving SOMAVERT and somatostatin analogues (drugs used to treat acromegaly) may increase risk of liver problems.

#### PROPER USE OF THIS MEDICATION

SOMAVERT is intended for subcutaneous (under the skin) administration. Your first dose, called a loading dose, will be given to you by a health care professional. Following this, your health care professional will instruct you to inject SOMAVERT subcutaneously once a day. You and any caregiver who may give you the injections should receive individual training under the supervision of the prescribing doctor.

Always follow the detailed instructions that are given below (INSTRUCTIONS FOR USE) when you are preparing or injecting SOMAVERT. However, these instructions do not replace the individual training by a health care professional.

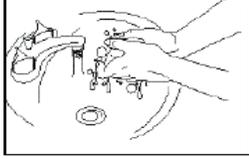
#### INSTRUCTION FOR USE

SOMAVERT is packaged in dry powdered form. Before you use SOMAVERT, it must first be reconstituted. This means it is mixed with a liquid called a diluent. The diluent is in the same packaging with the medicine. It is called Sterile Water for Injection, Ph. Eur. It is the only approved diluent for reconstituting SOMAVERT. Do not use any other liquid to reconstitute the medicine.

Use only one dose from each vial (small bottle) of SOMAVERT.

### Getting Started

Remove one package of **SOMAVERT** from the refrigerator and allow it to warm up to room temperature for approximately 10 minutes while you get ready to prepare your injection.



1. Wash your hands with soap and warm water. Dry your hands well.

Peel open the packaging to make it easier to pick up each item as you prepare for your injection. Do not use the vials if:

- they are damaged or faulty;
- the expiration date has passed;
- it has been frozen, even if it has now thawed.

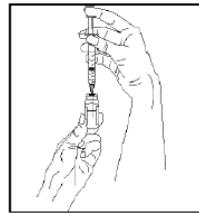


2. Gather the necessary supplies:
  - The package of **SOMAVERT** that is now at room temperature, which contains one vial of powder (**SOMAVERT**) and one vial of liquid (Sterile Water for Injection, Ph. Eur.)
  - One 1-cc syringe, or 3-cc syringe with a 21-gauge, 1-inch detachable needle (this will be the "diluent syringe")
  - One 1-cc syringe or 3-cc syringe, with a 27- to 30-gauge, ½-inch needle that is permanently attached to the syringe (this is the syringe you will use for the injection)
  - Alcohol or antiseptic swabs
  - Proper container for throwing away used needles.

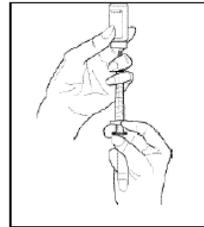


3. Remove the protective plastic caps from the tops of both vials (medicine and diluent). Take care not to touch the rubber vial stoppers. At this point, the stoppers are clean. If the stoppers are touched by anything, you must clean them with an antiseptic or alcohol swab before use.

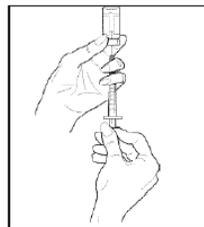
Carefully remove the cap from the detachable needle and set the cap aside. This needle is used in the diluent syringe.



4. Pull the plunger of the diluent syringe out to the 1-cc mark. With one hand, firmly hold the vial of diluent. With the other hand, push the needle of the diluent syringe straight through the center of the rubber stopper and deep into the vial. Gently push the plunger in until the air is injected into the vial.



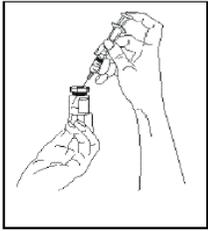
5. Firmly hold the diluent vial and syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and syringe together upside down. Bring them to eye level.



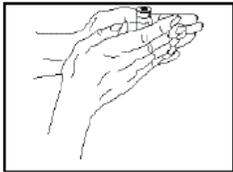
6. Slide one hand carefully down the diluent vial so that with your thumb and forefinger you can firmly hold the neck of the vial, and with your other fingers you can hold the upper part of the syringe. With the other hand, slowly pull the syringe plunger out to slightly past the 1-cc mark.

Check the syringe for air bubbles. If you see bubbles, tap the syringe barrel until the bubbles rise to the top of the syringe. Carefully push the plunger in to push only the air bubbles back into the vial. Recheck that 1 cc of diluent remains in the syringe. Then, pull the needle out of the vial. The vial should still have a lot of diluent in it. **Do not use the leftover diluent.**

### Reconstituting SOMAVERT



7. Push the needle of the diluent syringe straight through the stopper of the vial of **SOMAVERT** (the one with the powder). Tilt the syringe to the side and gently push the plunger in to inject the diluent down the inner side of the vial of **SOMAVERT**. Be sure the diluent does not fall directly on the powder, but flows down the inside wall of the vial. When the diluent syringe is empty, pull the needle out from the vial. Throw away the diluent vial with the leftover liquid in it, and also the diluent syringe and needle as directed by your health care professional. To help prevent injury, recap the needle only if instructed to do so by your health care professional, and in the way you were told to do so by your health care professional.



8. Hold the vial of **SOMAVERT** upright between your hands and gently roll it to dissolve the powder. **Do not shake the vial, as shaking may inactivate the medicine.** The mixture should be clear after the powder is dissolved. Do not inject the mixture if it appears cloudy or hazy, slightly colored, or if solid particles are visible. Tell your pharmacist and ask for a replacement vial. Do not throw the vial away because the pharmacist may ask that you return it. **Inject SOMAVERT within 3 hours of mixing it. If you wait more than 3 hours, you must throw away the mixture without injecting it.**

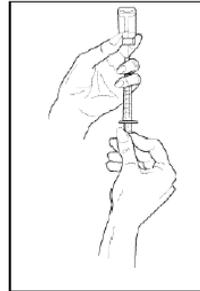
**Preparing the Injection**



9. Clean the rubber stopper of the vial of **SOMAVERT** with an antiseptic or alcohol swab. Carefully remove the cap from the syringe (the one with the permanently attached needle) and set the cap aside. Pull the syringe plunger out to the 1-cc mark. With one hand, firmly hold the vial. With the other hand, push the needle straight through the center of the rubber stopper and

deep into the vial. Gently push the plunger in until the air is injected into the vial.

Firmly hold the vial and syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and syringe together upside down. Bring them to eye level.



10. As before, slide one hand carefully down the vial so that with your thumb and forefinger you can firmly hold the neck of the vial, and with your other fingers you can hold the upper part of the syringe. With the other hand, slowly pull the syringe plunger out to withdraw the full contents of the vial (1 cc). To keep the needle tip within the mixture, you may have to pull the needle out of the stopper slowly as you draw out the liquid.

11. Check the syringe for air bubbles. If you see bubbles, tap the syringe barrel until the bubbles rise to the top of the syringe. Carefully push the plunger in to push only the air bubbles back into the vial. Recheck that 1 cc of the mixture remains in the syringe. Then pull the needle out of the vial.

Recap the needle as directed by your health care professional to help prevent injury while preparing the site for injection.

**Giving the Injection**

Subcutaneous (under the skin) injection sites may include the upper arm, lower back, upper thigh, abdomen (stomach area) and buttocks. Select the injection site from one of the areas identified by your health care professional. Select a different injection site each day so lumps do not develop. It may be helpful to keep a record of each day's injection site as you take your daily dose of **SOMAVERT**. Do not use an area that has a rash or broken skin, or is bruised or lumpy.



12. Prepare the injection site area as instructed by your health care professional. If you clean the site with an antiseptic or alcohol, let the skin dry before injecting the medicine. Uncap the needle if it was recapped.



13. With one hand, gently pinch up the skin at the site of injection. Hold the syringe with the other hand. In a single, smooth motion, push the needle completely into the skin straight down, at a 90-degree angle.

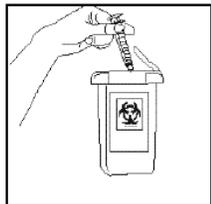


14. Be sure to keep the needle all the way into the skin while you slowly push the syringe plunger in until the barrel is empty.

Release the pinched skin. Wait 3 to 5 seconds and then pull the needle straight out.



15. Do not rub the injection area. A small amount of bleeding may occur. If necessary, apply a clean, dry cotton swab over the area and press gently for 1 or 2 minutes, or until the bleeding has stopped.



16. Safely throw away needles as directed by your health care professional, according to local environmental health regulations.

Your health care professional or pharmacist can give you information about throwing away the needles correctly. Be certain to store and throw away your treatment materials in a way that reduces danger to others.

**Overdose:**

In cases of overdose, administration of **SOMAVERT** should be discontinued and not resumed. If you have taken more **SOMAVERT** than you should, contact your doctor or a poison control centre immediately.

**Missed Dose:**

If you forget to give yourself an injection of **SOMAVERT**, get back on the schedule the next day. Do not inject a double dose to make up for a forgotten injection.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

**SOMAVERT** is generally well tolerated. The side effects are usually mild and do not last long. The following is not a complete list of side effects. Ask your doctor to tell you about the other side effects.

The most common side effects related to the use of the drug are pain, infection, reaction at the site of injection, influenza, and nausea.

Mild to serious allergic (anaphylactic) reactions have been reported in some patients taking **SOMAVERT**. Symptoms of a serious allergic reaction may include one or more of the following: swelling of the face, tongue, lips, or throat; wheezing or trouble breathing (spasm of the larynx); generalized skin rash, nettle rash (urticaria) or itching; or dizziness. Contact your doctor immediately if you develop any of these symptoms.

Caution and close monitoring by your doctor should be exercised when re-initiating **SOMAVERT** therapy.

A small number of patients who have used **SOMAVERT** have developed liver problems. Immediately stop therapy with **SOMAVERT** and contact your doctor if you notice any of the following:

- Sudden yellowing of the skin or whites of the eyes, or darkening of the urine
- Unexplained fatigue, nausea, vomiting, or pain in the abdomen (stomach area).

Your doctor will draw some of your blood before and during treatment with **SOMAVERT** to check how you are responding to the medicine, to change the dose if necessary, and to check for potential liver problems.

Some patients may develop changes in their blood sugar level. You doctor may change your dose of diabetes medicine while you take **SOMAVERT**.

Some patients may develop skin thickening at the injection site that could lead to lumps (lipohypertrophy).

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

**HOW TO STORE IT**

Until you mix the powder and the liquid, store the package of **SOMAVERT** in a refrigerator (2 to 8°C). Protect it from freezing.

After reconstitution (mixing the powder and liquid), you may keep the mixed medicine at room temperature inside the vial but you must inject the mixed **SOMAVERT** within 3 hours. If

you have not used the mixed medicine within 3 hours, throw it away.

### **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:

By toll-free telephone: 1-866-234-2345

By toll-free fax: 1-866-678-6789

Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:

Canada Vigilance Program

Health Canada

Postal Locator 1908C

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](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

### **MORE INFORMATION**

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<http://www.pfizer.ca>

or by calling 1-800-463-6001

This leaflet was prepared by Pfizer Canada ULC

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