

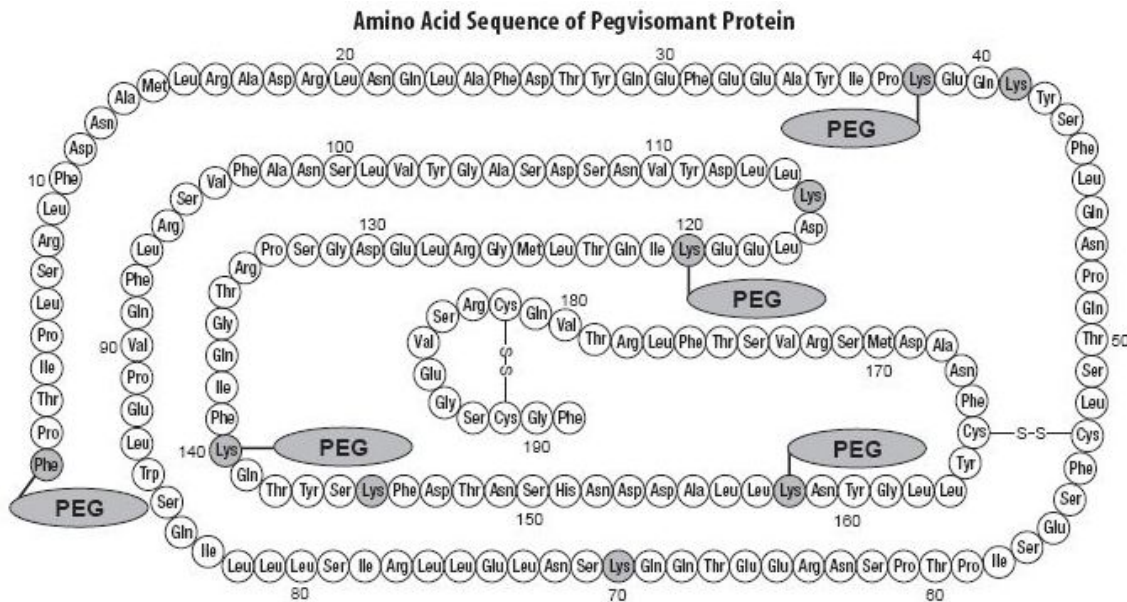
pegvisomant for injection

R_y only

DESCRIPTION

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

Pegvisomant is a protein of recombinant DNA origin containing 191 amino acid residues to which several polyethylene glycol (PEG) polymers are covalently bound (predominantly 4 to 6 PEG/protein molecule). The molecular weight of the protein of pegvisomant is 21,998 Daltons. The molecular weight of the PEG portion of pegvisomant is approximately 5000 Daltons. The predominant molecular weights of pegvisomant are thus approximately 42,000, 47,000, and 52,000 Daltons. The schematic shows the amino acid sequence of the pegvisomant protein (PEG polymers are shown attached to the 5 most probable attachment sites). Pegvisomant is synthesized by a specific strain of *Escherichia coli* bacteria that has been genetically modified by the addition of a plasmid that carries a gene for GH receptor antagonist. Biological potency is determined using a cell proliferation bioassay.



Stippled residues indicate PEG attachment sites (Phe₁, Lys₃₈, Lys₄₁, Lys₇₀, Lys₁₁₅, Lys₁₂₀, Lys₁₄₀, Lys₁₄₅, Lys₁₅₈)

SOMAVERT is supplied as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of Sterile Water for Injection, USP. SOMAVERT is available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant

protein (approximately 10, 15, and 20 U activity, respectively). Vials containing 10, 15, and 20 mg of pegvisomant protein correspond to approximately 21, 32, and 43 mg pegvisomant, respectively. Each 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 phosphate monobasic monohydrate.

SOMAVERT is supplied in packages that include a vial containing diluent. Sterile Water for Injection, USP, is a sterile, nonpyrogenic preparation of water for injection that contains no bacteriostat, antimicrobial agent, or added buffer, and is supplied in single-dose containers to be used as a diluent.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pegvisomant selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with GH signal transduction. 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 IGF binding protein-3 (IGFBP-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. After a single subcutaneous administration, exposure (C_{max} , AUC) to pegvisomant increases disproportionately with increasing dose. Mean \pm SEM serum pegvisomant concentrations after 12 weeks of therapy with daily doses of 10, 15, and 20 mg were 6600 ± 1330 ; $16,000 \pm 2200$; and $27,000 \pm 3100$ ng/mL, respectively.

Metabolism and Elimination: The pegvisomant molecule contains covalently bound polyethylene glycol polymers in order to reduce the clearance rate. Clearance of pegvisomant following multiple doses is lower than seen following a single dose. The mean total body systemic clearance of pegvisomant following multiple doses is estimated to range between 36 to 28 mL/h for subcutaneous doses ranging from 10 to 20 mg/day, respectively. Clearance of pegvisomant was found to increase with body weight. Pegvisomant is eliminated from serum with a mean half-life of approximately 6 days following either single or multiple doses. Less than 1% of administered drug is recovered in the urine over 96 hours. The elimination route of pegvisomant has not been studied in humans.

Drug-Drug Interactions

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not

receiving opioids. The mechanism of this interaction is not known (see **PRECAUTIONS, Drug Interactions**).

Special Populations

Renal: No pharmacokinetic studies have been conducted in patients with renal insufficiency.

Hepatic: No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Geriatric: No pharmacokinetic studies have been conducted in elderly subjects.

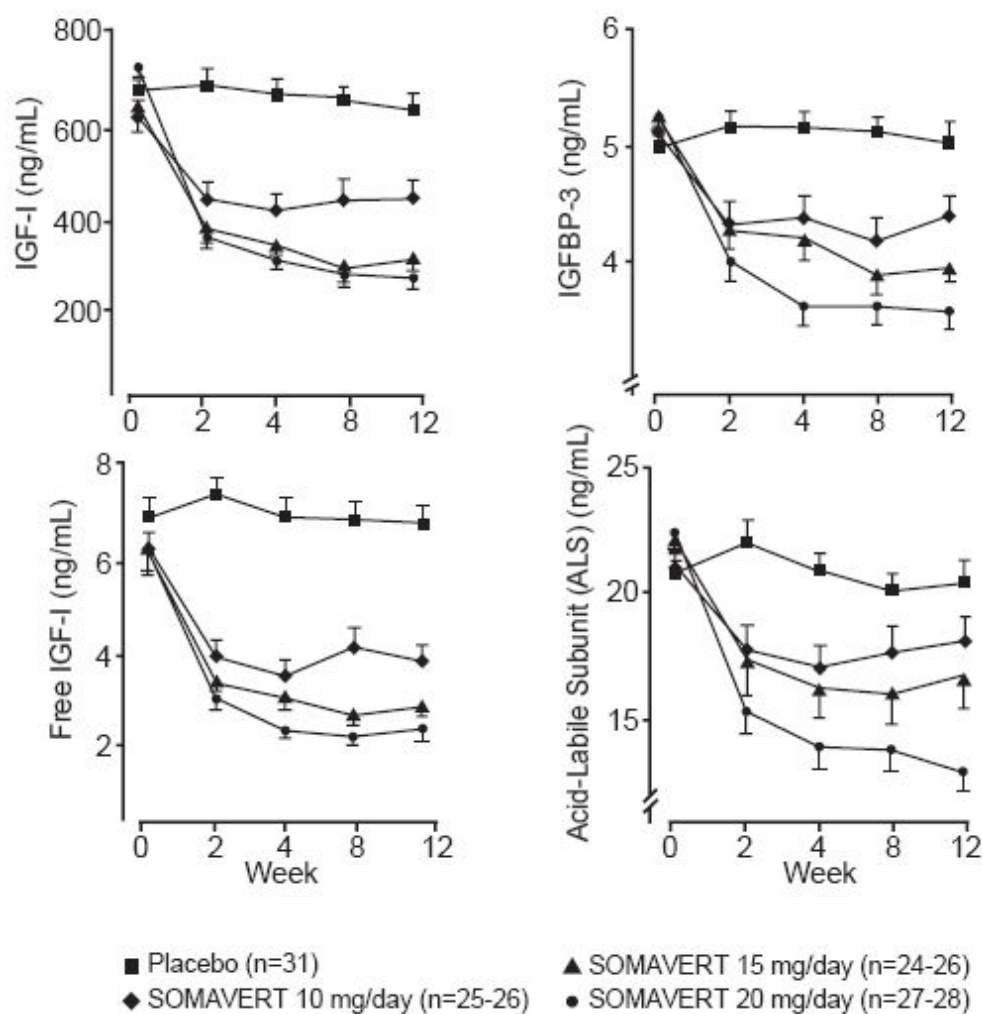
Pediatric: No pharmacokinetic studies have been conducted in pediatric subjects.

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

Race: The effect of race on the pharmacokinetics of pegvisomant has not been studied.

CLINICAL STUDIES

One hundred twelve patients with acromegaly previously treated with surgery, radiation therapy, or medical therapies participated in a 12-week, randomized, double-blind, multi-center study comparing placebo and SOMAVERT. Following withdrawal from previous medical therapy, the 80 patients randomized to treatment with SOMAVERT received a subcutaneous (SC) loading dose, followed by 10, 15, or 20 mg/day SC. The three groups that received SOMAVERT showed dose-dependent 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 1).



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

After 12 weeks of treatment, serum IGF-I levels were normalized in 10%, 39%, 75%, and 82% of subjects treated with placebo, 10, 15, or 20 mg/day of SOMAVERT, respectively (Figure 2).

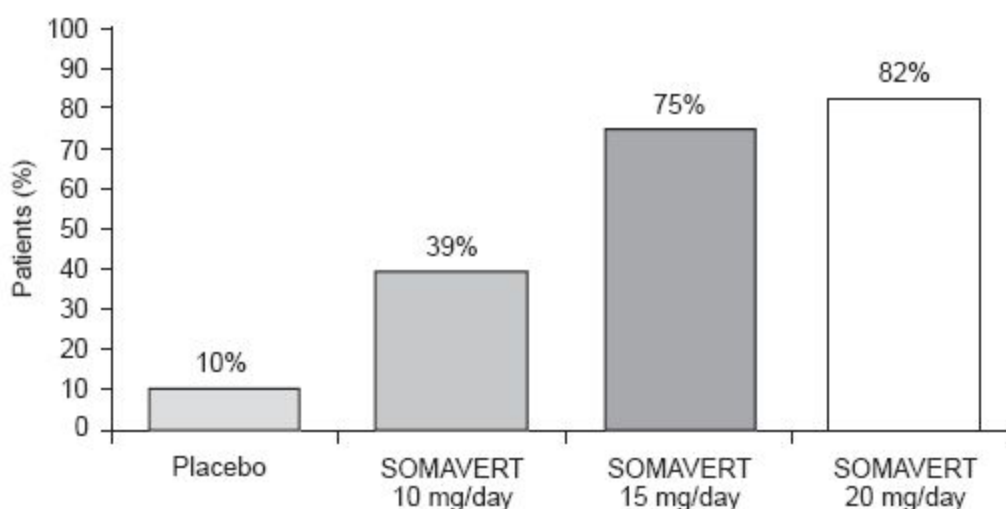


Figure 2. Percent of Patients Whose IGF-I Levels Normalized at Week 12

Table 2 shows the effect of treatment with SOMAVERT on ring size (standard jeweler's sizes converted to a numeric score ranging from 1 to 63), and on both the total and individual scores for signs and symptoms of acromegaly. Each individual score (for soft-tissue swelling, arthralgia, headache, perspiration and fatigue) was based on a nine-point ordinal rating scale (0 = absent and 8 = severe and incapacitating), and the total score was derived from the sum of the individual scores. Mean baseline scores were as follows: ring size = 47.1; total signs and symptoms = 15.2; soft tissue swelling = 2.5; arthralgia = 3.2; headache = 2.4; perspiration = 3.3; and fatigue = 3.7.

Table 1. Mean Percent Change from Baseline in IGF-I at Week 12 for Intent-to-Treat Population

	SOMAVERT			Placebo n=31
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
Mean percent change from baseline in IGF-I (SD)	-27 (28)	-48 (26)	-63 (21)	-4.0 (17)
SOMAVERT minus Placebo (95% CI for treatment difference)	-23* (-35, -11)	-44* (-56, -33)	-59* (-68, -49)	

* P<0.01

Table 2. Mean Change from Baseline (SD) 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	
Ring size	-0.8 (1.6)	-1.9 (2.0)	-2.5 (3.3)	-0.1 (2.3)

Total score for signs and symptoms of acromegaly	-2.5 (4.3)	-4.4 (5.9)	-4.7 (4.7)	1.3 (6.0)
Soft-tissue swelling	-0.7 (1.6)	-1.2 (2.3)	-1.3 (1.3)	0.3 (2.3)
Arthralgia	-0.3 (1.8)	-0.5 (2.5)	-0.4 (2.1)	0.1 (1.8)
Headache	-0.4 (1.6)	-0.3 (1.4)	-0.3 (2.0)	0.1 (1.7)
Perspiration	-0.6 (1.6)	-1.1 (1.3)	-1.7 (1.6)	0.1 (1.7)
Fatigue	-0.5 (1.4)	-1.3 (1.7)	-1.0 (1.6)	0.7 (0.5)

Ring size at week 12 was smaller (improved) in the groups treated with 15 or 20 mg of SOMAVERT, compared with placebo. The mean total score for signs and symptoms at week 12 was lower (improved) in each of the groups treated with SOMAVERT, compared with the group treated with placebo.

Serum growth hormone (GH) concentrations, as measured by research assays using antibodies that do not cross-react with pegvisomant (see **PRECAUTIONS, Drug/Laboratory Test 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 a 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.

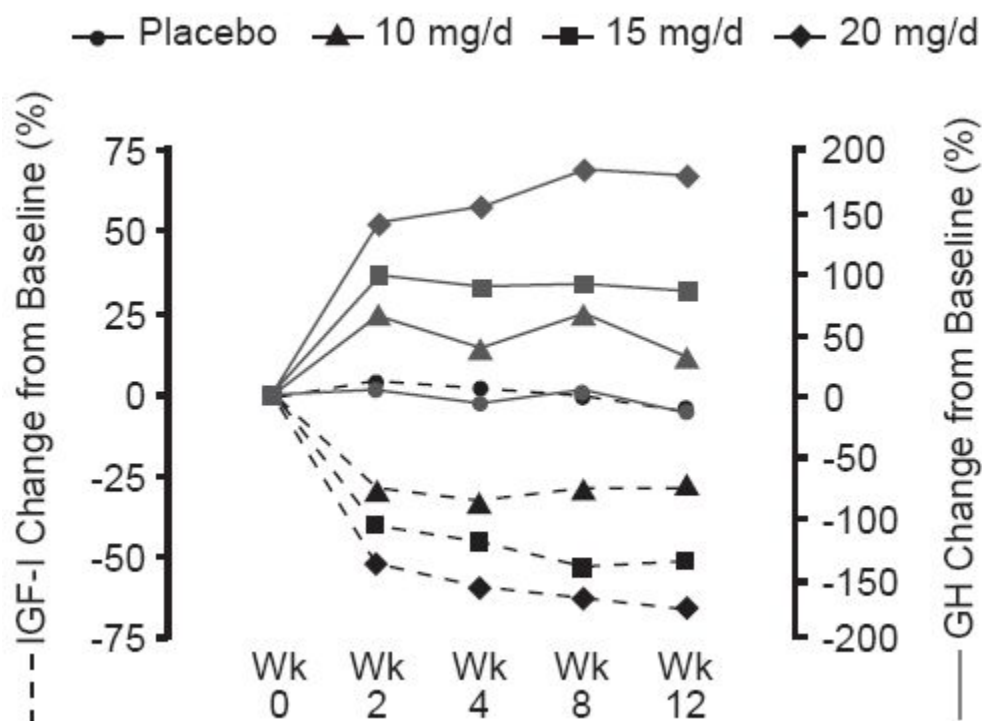


Figure 3. Percent Change in Serum GH and IGF-I Concentrations

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 = 55 weeks). The mean (\pm standard deviation) IGF-I concentration at baseline in this cohort was 917 (\pm 356) ng/mL after withdrawal from previous medical therapy, falling to 268 (\pm 134) ng/mL at the end of treatment with SOMAVERT. Thirty-five of the 38 patients (92%) 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.

INDICATIONS AND USAGE

SOMAVERT is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery, and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum IGF-I levels.

CONTRAINDICATIONS

SOMAVERT is contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS

General

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, 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.

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 none of the patients with acromegaly and with diabetes mellitus who were treated with SOMAVERT during the clinical studies had clinically relevant hypoglycemia, these patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary.

GH Deficiency: A state of functional GH deficiency may result from administration of SOMAVERT, despite the presence of elevated serum GH levels. Therefore, during treatment with SOMAVERT, patients should be carefully observed for the clinical signs and symptoms of a GH-deficient state, and serum IGF-I concentrations should be monitored and maintained within the age-adjusted normal range (by adjustment of the dose of SOMAVERT).

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%) exposed to 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.

Baseline serum ALT, AST, TBIL, and ALP levels should be obtained prior to initiating therapy with SOMAVERT. Table 3 lists recommendations regarding initiation of treatment with SOMAVERT, based on the results of these liver tests (LTs).

Table 3. Initiation of Treatment with SOMAVERT Based on Results of Liver Tests

Baseline LT Levels	Recommendations
Normal	May treat with SOMAVERT. Monitor LTs at monthly intervals during the first 6 months of treatment, quarterly for the next 6 months, and then semi-annually for the next year.
Elevated, but less than or equal to 3 times ULN	May treat with SOMAVERT; however, monitor LTs monthly for at least one year after initiation of therapy and then semi-annually for the next year.
Greater than 3 times ULN	Do not treat with SOMAVERT 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 SOMAVERT. If the decision is to treat, LTs and clinical symptoms should be monitored very closely.

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 4).

Table 4. Continuation of Treatment with SOMAVERT Based on Results of Liver Tests

LT Levels and Clinical Signs/Symptoms	Recommendations
Greater than or equal to 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 SOMAVERT. 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 SOMAVERT 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 SOMAVERT, 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)	Immediately perform a comprehensive hepatic workup. If liver injury is confirmed, the drug should be discontinued.

Lipohypertrophy

Lipohypertrophy has been reported in <5% of patients following pegvisomant administration.

Systemic Hypersensitivity

In subjects with systemic hypersensitivity reactions, caution and close monitoring should be exercised when re-initiating Somavert therapy. (See **ADVERSE REACTIONS, Post-Marketing Experience**)

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 enclosed instructions).

Patients should be informed about the need for serial monitoring of LTs, and told to immediately discontinue therapy and contact their physician if they become jaundiced. 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.

Patients should be instructed in the technique and importance of proper disposal of materials used for the administration of SOMAVERT (e.g., needles and syringes, medical waste, vial). Patients should be cautioned against reuse of needles.

Laboratory Tests

Liver Tests: Recommendations for monitoring LTs are stated above (see **PRECAUTIONS, 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/Laboratory Test Interactions**). Furthermore, even when accurately determined, GH levels usually increase during therapy with SOMAVERT. Therefore, treatment with SOMAVERT should not be adjusted based on serum GH concentrations.

Drug Interactions

Patients with acromegaly and 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.

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known.

Drug/Laboratory Test 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pegvisomant was administered subcutaneously to rats daily for 2 years at doses of 2, 8 and 20 mg/kg (about 2, 10 and 25-fold a single 20mg dose in humans on an AUC basis). Long term treatment with pegvisomant at 8 and 20 mg/kg caused an increase in malignant fibrous histiocytoma at injection sites in males. Injection site tumors were not seen in female rats at the same doses. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections.

Pegvisomant did not cause genetic damage in standard *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration).

Pegvisomant was found to have no effect on fertility or reproductive performance of female rabbits at subcutaneous doses up to 10 mg/kg/day (10-fold the recommended human dose on a body surface area basis).

Pregnancy: Pregnancy Category B

Early embryonic development and teratology studies were conducted in pregnant rabbits with pegvisomant at subcutaneous doses of 1, 3, and 10 mg/kg/day. There was no evidence of teratogenic effects associated with pegvisomant treatment during organogenesis. At the 10-mg/kg/day dose (10 times the maximum human therapeutic dose based on body surface area), a reproducible, slight increase in post-implantation loss was observed in both studies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, SOMAVERT should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Clinical studies of SOMAVERT did not include sufficient numbers of subjects aged 65 and over to determine whether they 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.

ADVERSE REACTIONS

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-approval clinical studies (see **PRECAUTIONS, Liver Tests [LTs]**).

General

Nine patients with acromegaly (9.6%) withdrew from pre-marketing clinical studies because of adverse events, including two patients with marked transaminase elevations (see **PRECAUTIONS, Liver Tests [LTs]**), one patient with lipohypertrophy at the injection sites, and one patient with substantial weight gain. The majority of reported adverse events were of limited duration. Most adverse events did not appear to be dose dependent. Table 5 shows the incidence of treatment-emergent adverse events that were reported in at least two patients treated with SOMAVERT and at frequencies greater than placebo during the 12-week, placebo-controlled study.

Table 5. Number of Patients (%) with Acromegaly Reporting Adverse Events in a 12-week Placebo-controlled Study with SOMAVERT*

Event	SOMAVERT			Placebo n=32
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
Body as a whole				
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
Accidental injury	2 (8%)	1 (4%)	0	1 (3%)
Back pain	2 (8%)	0	1 (4%)	1 (3%)
Flu syndrome	1 (4%)	3 (12%)	2 (7%)	0
Chest pain	1 (4%)	2 (8%)	0	0
Digestive				
Abnormal liver function tests	3 (12%)	1 (4%)	1 (4%)	1 (3%)
Diarrhea	1 (4%)	0	4 (14%)	1 (3%)
Nausea	0	2 (8%)	4 (14%)	1 (3%)
Nervous				
Dizziness	2 (8%)	1 (4%)	1 (4%)	2 (6%)
Paresthesia	0	0	2 (7%)	2 (6%)
Metabolic and nutritional disorders				
Peripheral edema	2 (8%)	0	1 (4%)	0
Cardiovascular				
Hypertension	0	2 (8%)	0	0
Respiratory				
Sinusitis	2 (8%)	0	1 (4%)	1 (3%)

* 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).

Immunogenicity

In pre-marketing clinical studies, approximately 17% of the patients developed low titer, non-neutralizing anti-GH antibodies. Although the presence of these antibodies did not appear to impact the efficacy of SOMAVERT, the long-term clinical significance of these antibodies is not known. No assay for anti-pegvisomant antibodies is commercially available for patients receiving SOMAVERT.

Post-Marketing Experience

Lipohypertrophy has been reported in <5% of patients following pegvisomant administration.

Asymptomatic, transient elevations in transaminases up to 15 times ULN have been observed in <2% of patients in the post-marketing experience. These reports were not associated with an increase in bilirubin, and there were no clinical consequences for these patients. Transaminase elevations normalized with time, most often after suspending treatment (SOMAVERT should be used in accordance with the information presented in Table 4 with respect to liver test abnormalities).

Systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalized skin reactions (rash, erythema, pruritus, urticaria) have been reported in post-marketing use. Some patients required hospitalization. Symptoms did not re-occur in all patients after re-challenge (See **PRECAUTIONS**)

OVERDOSAGE

In one reported incident of acute overdose with SOMAVERT during pre-marketing clinical studies, 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.

Drug Abuse and Dependence

Available data do not demonstrate drug-abuse potential or psychological dependence with SOMAVERT. Radiolabeled pegvisomant does not cross the blood-brain barrier in rats.

DOSAGE AND ADMINISTRATION

A loading dose of 40 mg of SOMAVERT should be administered subcutaneously under physician supervision. The patient should then be instructed to begin daily subcutaneous injections of 10 mg of SOMAVERT. Serum IGF-I concentrations should be measured every four to six weeks, at which time the dosage of SOMAVERT should be adjusted in 5-mg increments if IGF-I levels are still elevated (or 5-mg decrements if IGF-I levels have decreased below the normal range). While the goals of therapy are to achieve (and then maintain) serum IGF-I concentrations within the age-adjusted normal range and to alleviate the signs and symptoms of acromegaly, titration of dosing should be based on IGF-I levels. Patients should be advised to avoid doubling up of dose should an injection be missed but to receive an injection at their next regularly scheduled dose and continue further treatment as recommended by their health care provider. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I levels would benefit from increased dosing with SOMAVERT.

The maximum daily maintenance dose should not exceed 30 mg.

SOMAVERT is supplied as a lyophilized powder. Each vial of SOMAVERT should be reconstituted with 1 mL of the diluent provided in the package (Sterile Water for

Injection, USP). Instructions regarding reconstitution and administration are included in the package of SOMAVERT and should be closely followed. To prepare the solution, withdraw 1 mL of Sterile Water for Injection, USP 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. Discard the diluent vial containing the remaining water for injection. After reconstitution, each vial of SOMAVERT contains 10, 15, or 20 mg of pegvisomant protein in one 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 six hours after reconstitution.

Pegvisomant may be given in the thigh, buttocks, upper arm, or abdomen; the site of SC injections should be rotated daily to help prevent lipohypertrophy.

HOW SUPPLIED

SOMAVERT is available in single-dose, sterile glass vials in the following strengths:

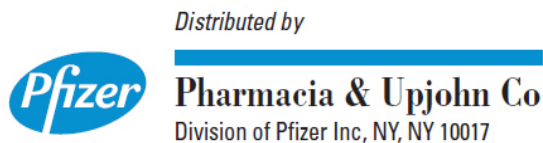
10 mg (as protein) vial	NDC 0009-5176-01
15 mg (as protein) vial	NDC 0009-5178-01
20 mg (as protein) vial	NDC 0009-5180-01

Each package of SOMAVERT also includes a single-dose vial containing Sterile Water for Injection, USP.

Storage

Prior to reconstitution, SOMAVERT should be stored in a refrigerator at 36 to 46°F (2 to 8°C). Protect from freezing.

After reconstitution, SOMAVERT may be stored at room temperature [59 to 77 °F (15 to 25 °C)] but should be administered within six hours. Only one dose should be administered from each vial.



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Dublin, Ireland**

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PATIENT INFORMATION

SOMAVERT® (SOM-ah-vert) pegvisomant for injection

Read this Patient Information before you start receiving Somavert and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is SOMAVERT?

SOMAVERT is a prescription medicine used to treat people who have too much growth hormone (acromegaly). SOMAVERT is used to treat people with symptoms of acromegaly who are not able to be treated or have not already been helped by:

- surgery
- radiation therapy
- other medical therapies

It is not known if SOMAVERT is safe and effective in children.

Who should not take SOMAVERT?

Do not take SOMAVERT if you are allergic to pegvisomant or any of the other ingredients in SOMAVERT. See the end of this leaflet for a complete list of ingredients in SOMAVERT.

What should I tell my healthcare provider before I take SOMAVERT?

Before you take SOMAVERT, tell your healthcare provider if you:

- have diabetes
- have or have had liver problems
- are pregnant or plan to become pregnant. It is not known if SOMAVERT will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOMAVERT passes into your breast milk. You and your health care provider should decide if you will take SOMAVERT or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

SOMAVERT may affect the way other medicines work, and other medicines may affect how SOMAVERT works. Especially tell your healthcare provider if you take:

- insulin or other medicines used to treat diabetes
- narcotics (opioid medicines)

If you are not sure, ask your healthcare provider or pharmacist whether you take these medicines.

Know the medicines you take. Keep a list of all the medicines you take to show your healthcare providers and pharmacists when you get a new medicine.

How should I take SOMAVERT?

- Read the Instructions for Use at the end of this Patient Information for information about the right way to use SOMAVERT.
- SOMAVERT is given 1 time each day as an injection under your skin (subcutaneous).
- Your first injection of SOMAVERT should be given by your healthcare provider.
- Your healthcare provider will teach you or your caregiver how to inject SOMAVERT.
- If you take too much SOMAVERT, call your healthcare provider right away.
- If you miss a dose of SOMAVERT, just take the next dose at the regular time. Do **not** take 2 doses at the same time. If you are not sure about your dosing, ask your healthcare provider.
- Your healthcare provider will do blood tests every three to six months to check your liver and insulin-like growth factor-I (IGF-I) levels while you are taking SOMAVERT.

What are the possible side effects of SOMAVERT?

SOMAVERT may cause serious side effects, including:

- **changes in your blood sugar level.** Your healthcare provider may change your dose of diabetes medicine while you take SOMAVERT.
- **markedly reduced levels of IGF-1 in your body.** Your healthcare provider will do blood tests to check your IGF-1 levels in your body while you are taking SOMAVERT.
- **liver problems.** Stop injecting SOMAVERT right away and call your healthcare provider if you have any of the following symptoms of liver problems:
 - yellowing of your eyes (jaundice)
 - dark, amber-colored urine
 - feeling very tired (fatigue or exhaustion)
 - nausea and vomiting
 - pain in your stomach area (abdomen)
 - generalized swelling
 - bruising easily
- **allergic reactions.** Call your healthcare provider right away if you have any of the following symptoms of a serious allergic reaction:

- swelling of your face, tongue, lips, or throat
- wheezing or trouble breathing
- skin rash, redness, or swelling
- severe itching
- dizziness or fainting

The most common side effects of SOMAVERT include:

- pain
- infection
- reaction at the site of injection
- flu symptoms
- nausea
- diarrhea
- abnormal liver tests

These are not all of the possible side effects of SOMAVERT. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your health care provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SOMAVERT?

- **Before you mix the SOMAVERT powder and the liquid:**
 - Store SOMAVERT in a refrigerator between 36°F to 46°F (2°C to 8°C).
 - Do not freeze SOMAVERT.
- **After you mix the SOMAVERT powder and liquid:**
 - Keep the mixed SOMAVERT at room temperature between 59°F to 77°F (15°C to 25°C).
 - Keep SOMAVERT inside the vial or the syringe until you are ready to inject it.
 - **You must inject the mixed SOMAVERT within 6 hours after you mix it.**
 - If you have not used the mixed SOMAVERT within 6 hours, throw the SOMAVERT away.

Keep SOMAVERT and all medicines out of the reach of children.

General Information about the safe and effective use of SOMAVERT

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SOMAVERT for a condition for which it was not prescribed. Do not give SOMAVERT to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about SOMAVERT. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SOMAVERT that is written for health professionals.

For more information, go to www.Somavert.com or call 1-800-645-1280.

What are the ingredients in Somavert?

Active ingredient: pegvisomant, including polyethylene glycol

Inactive ingredients: glycine, mannitol, sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate

INSTRUCTIONS FOR USE
SOMAVERT® (SOM-ah-vert)
(pegvisomant for injection)

Supplies you need to give SOMAVERT. See Figure A.

- 1 package of SOMAVERT that contains:
 - 1 vial of powdered SOMAVERT medicine (powder vial)
 - 1 vial of liquid (diluent) labeled “Sterile Water for Injection, USP” to mix the powdered medicine

The vials in the package of SOMAVERT have stoppers that are not made with natural rubber latex.

The SOMAVERT package does not come with syringes and needles.

- a 1 mL syringe with a 21 gauge to 27 gauge needle that is at least 1 inch long. This is the syringe and needle needed to mix the medicine (diluent syringe).
- a 1 mL insulin syringe with attached needle. This is the syringe needed for your injection.
- 2 alcohol swabs
- 1 small clean, dry cotton pad
- 1 sharps container for throwing away used needles and syringes
- a clean, flat surface to work on, like a table

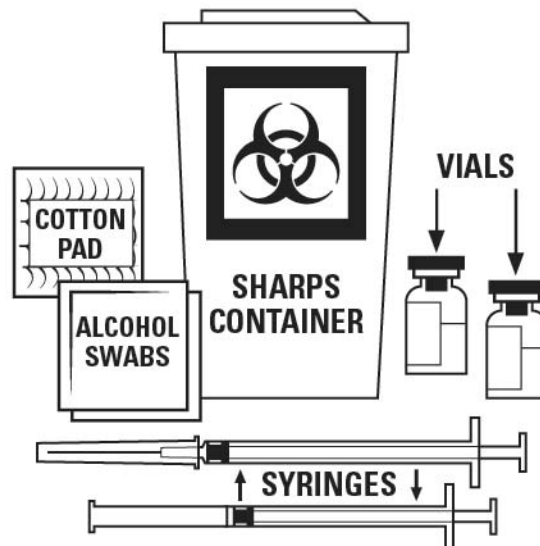


Figure A

Preparing and mixing your SOMAVERT medicine

The SOMAVERT medicine comes as a dry powder. Before you use SOMAVERT, you must mix the dry powder with the vial of diluent that comes in the SOMAVERT package.

Do not use any other liquid to mix the medicine.

Step 1. Remove 1 package of SOMAVERT from the refrigerator about 10 minutes before you plan to give your SOMAVERT injection. Let the SOMAVERT stand at room temperature to warm up the medicine.

Step 2. Wash your hands with soap and warm water. Dry your hands well.

Step 3. Remove the plastic caps from the tops of the powder vial and the diluent vial. See Figure B.
Do not touch the rubber vial stoppers. The stoppers are clean. If the stoppers are touched by anything, you must clean them with an alcohol swab before use.

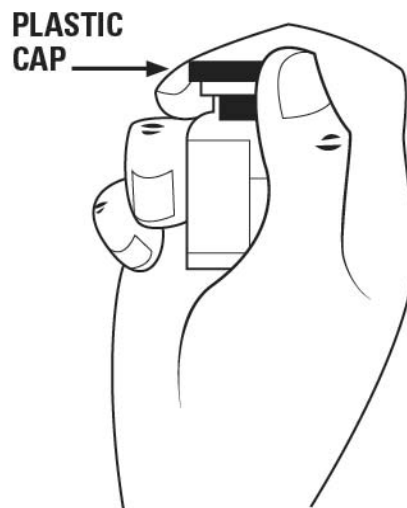


Figure B

Step 4. Carefully remove the cap from the diluent syringe with the larger needle and set the cap aside on the table. See Figure C.

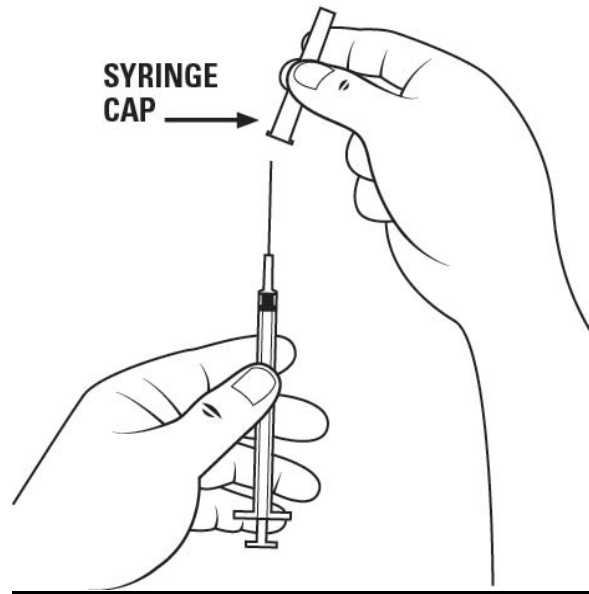


Figure C

Step 5. Pull the plunger of the diluent syringe out to the 1 mL mark. With 1 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. See Figure D.

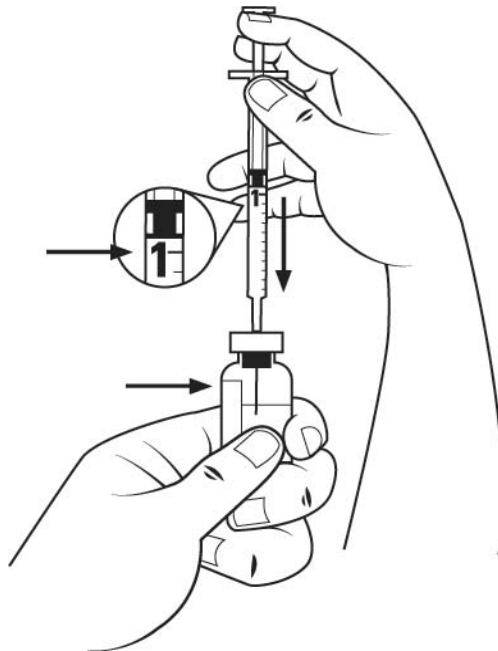


Figure D

Step 6. Firmly hold the diluent vial and syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and diluent syringe

together upside down. Hold them at eye level. See Figure E.

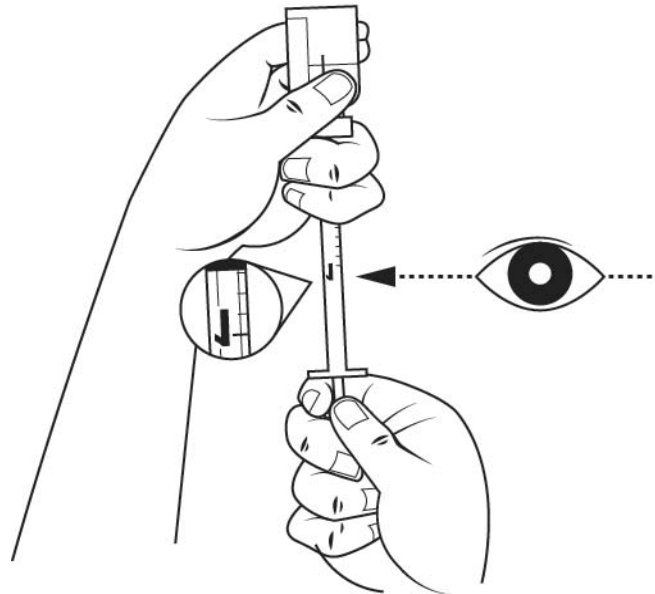


Figure E

Step 7. Slide 1 hand carefully down the diluent vial so you can firmly hold the neck of the vial with your thumb and forefinger. Hold the upper part of the syringe with your other fingers. With the other hand, slowly pull the plunger out to slightly past the 1 mL mark on the diluent syringe. See Figure F.

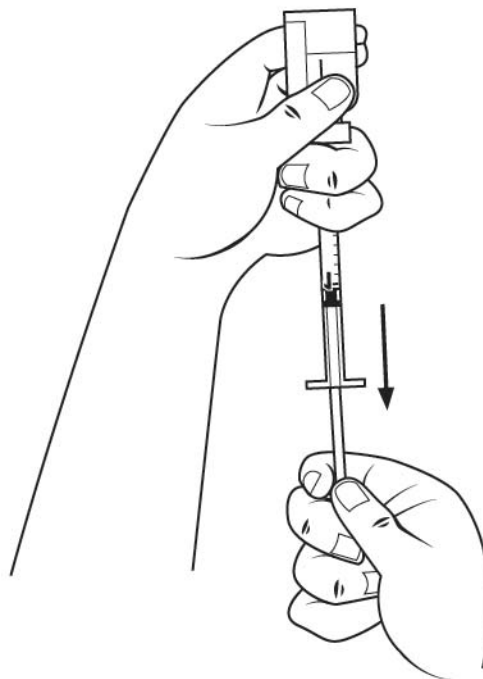


Figure F

Step 8. Check the diluent syringe for air bubbles. If you see bubbles, tap the diluent 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. See Figure G. If you push too much of the liquid back into the vial, pull the plunger out again to the 1 mL mark.

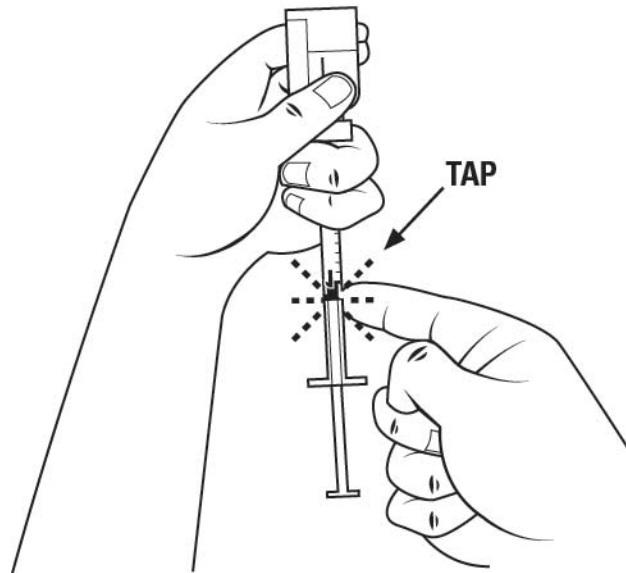


Figure G

Step 9. Make sure that 1 mL of diluent remains in the diluent syringe. Then, pull the needle out of the vial. The vial should still have diluent in it. **Do not use the leftover diluent in the vial.**

Step 10. Push the needle of the diluent syringe straight through the stopper of the vial of powdered SOMAVERT. Tilt the diluent syringe to the side and gently push the plunger in to inject the diluent down the inner side of the SOMAVERT powder vial. Be sure the diluent does not fall directly on the powder, but flows down the inside wall of the vial. See Figure H.

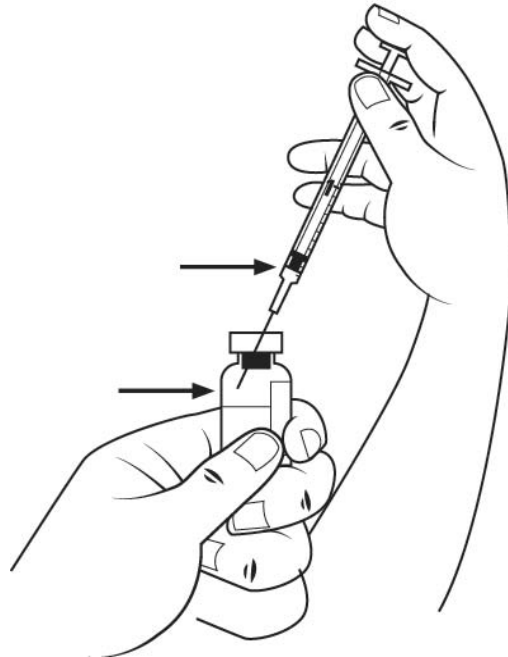


Figure H

Step 11. When the diluent syringe is empty, pull the needle out of the powder vial.

Throw away the diluent vial with the leftover liquid in it. Throw away the diluent syringe and needle in the sharps container as your healthcare provider told you.

Step 12. Hold the medicine vial of SOMAVERT upright between your hands and gently roll it to dissolve the powder into a solution. See Figure I.

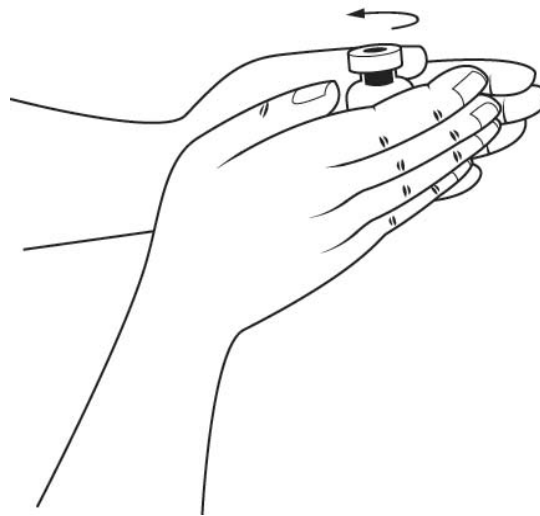


Figure I

- **Do not shake the medicine vial. Shaking may destroy the medicine.**
- The liquid medicine should be clear after the powder is dissolved. Do not inject the liquid medicine if it looks cloudy or hazy, slightly colored, or you see solid particles in it. Tell your pharmacist and ask for another vial. Do not throw the vial away because the pharmacist may ask that you return it.
- **Inject SOMAVERT within 6 hours of mixing it. If you wait more than 6 hours, you must throw away the medicine without injecting it.**
- **Each mixed medicine vial contains 1 dose of SOMAVERT. Do not split the liquid medicine into multiple doses.**

Preparing your SOMAVERT injection syringe

Step 13. Clean the rubber stopper of the vial of SOMAVERT with an alcohol swab.

- Carefully remove the cap from the insulin syringe and set the cap on the table.
- Pull the insulin syringe plunger out to the 1 mL mark. With 1 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 medicine vial. See Figure J.

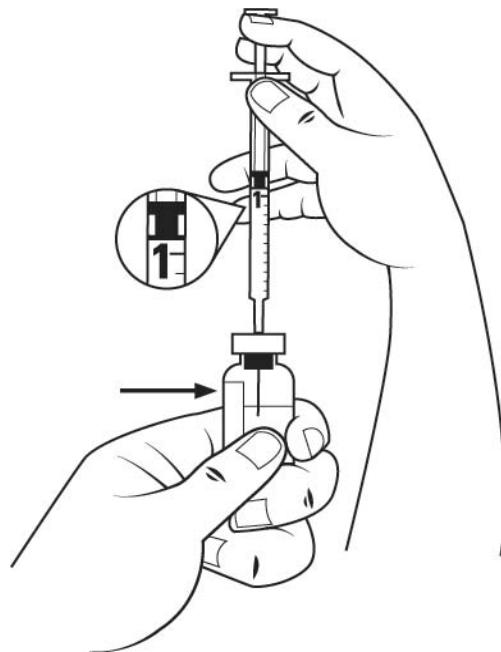


Figure J

Step 14. Firmly hold the medicine solution vial and insulin syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and syringe together upside down. Hold them at eye level. See Figure K.

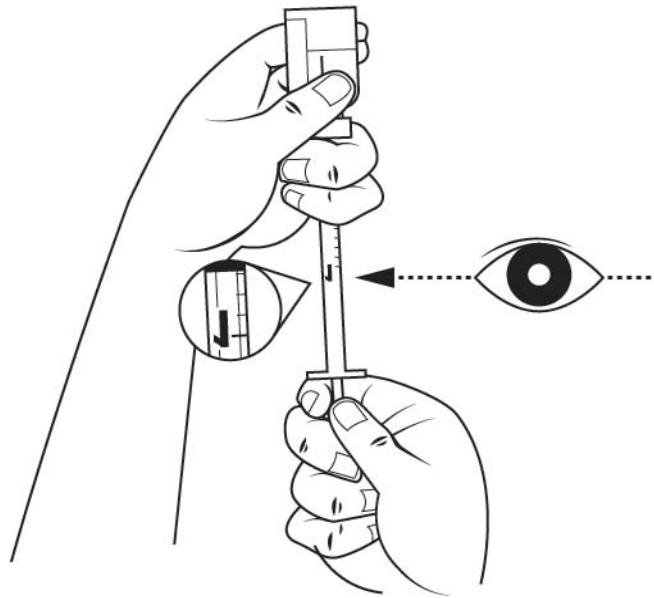


Figure K

Step 15. Slide 1 hand carefully down the medicine solution vial so you can firmly hold the neck of the vial with your thumb and forefinger. Hold the upper part of the syringe with your other fingers. With the other hand, slowly pull the plunger out to slightly past the 1 mL mark on the insulin syringe. See Figure L.

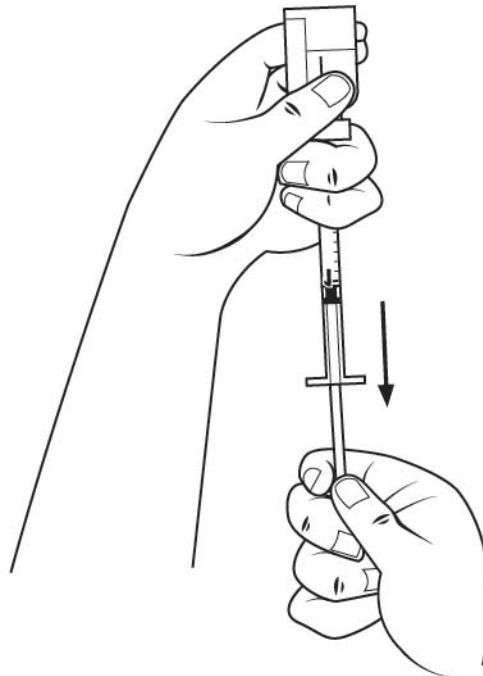


Figure L

Step 16. Check the insulin syringe for air bubbles. If you see bubbles, tap the insulin 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. See Figure M.

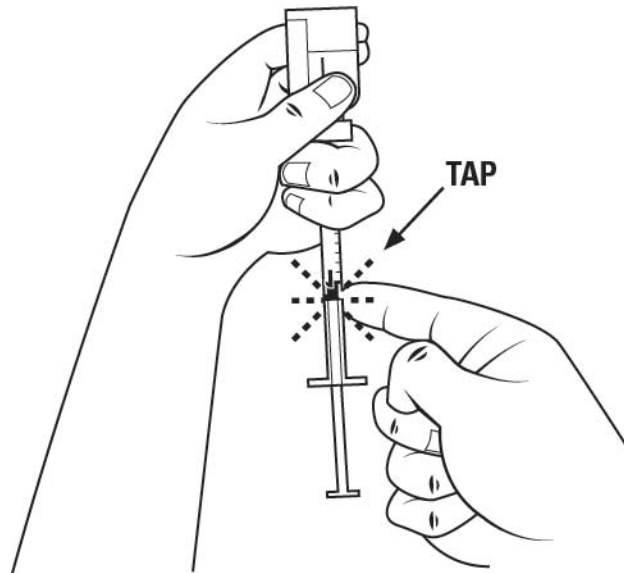


Figure M

Step 17. Withdraw the entire 1 mL of medicine solution from the vial. Slowly withdraw the needle to keep the tip in the liquid until you get all the medicine solution out of the vial. See Figure N.
Set the syringe and needle on the table without anything touching the needle.

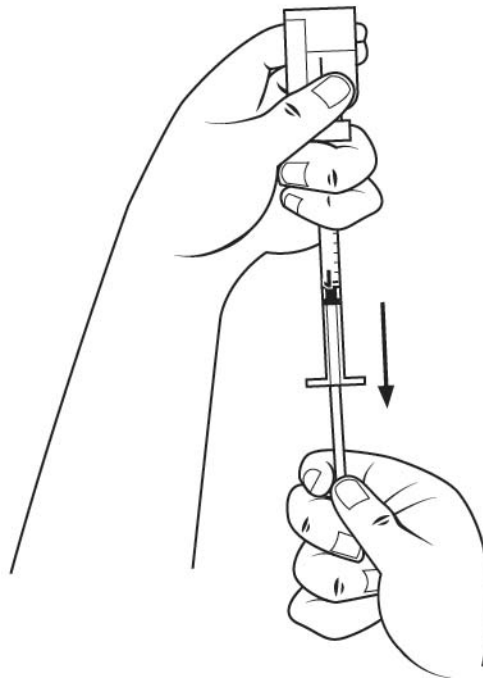


Figure N

Selecting your SOMAVERT injection site

Step 18. SOMAVERT is injected under the skin (subcutaneous). Injection sites may include your upper arm, upper thigh, stomach area (abdomen) and buttocks. See Figure O.

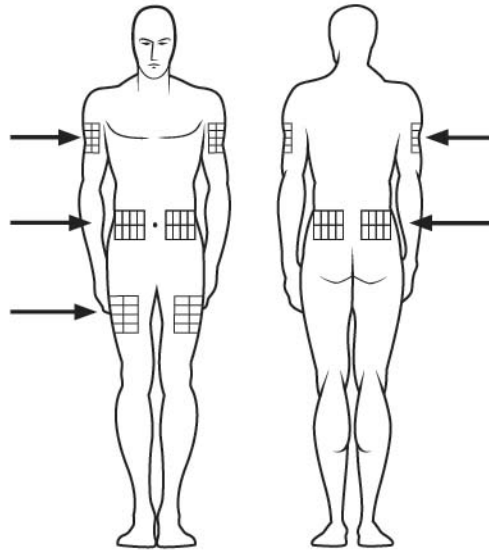


Figure O

- Choose your injection site from 1 of the areas your healthcare provider told you to use.
- Choose a different injection site each day so lumps do not develop in your skin. Keep a record of each day's injection site as you inject your daily dose of SOMAVERT.
- Do not use an area of your body that has:
 - a rash
 - broken skin
 - bruising
 - lumps in your skin

Giving your SOMAVERT injection

Step 19. Clean your injection site with an alcohol swab. See Figure P. Let your skin dry before you inject your medicine.



Figure P

Step 20. With 1 hand, gently pinch up your skin at your injection site. See Figure Q.



Figure Q

Step 21. Carefully pick up the insulin syringe with your other hand and hold it like a pen. In a single, smooth motion push the needle straight down and completely into your skin (at a 90-degree angle).

- Keep the needle pushed all the way into your skin while you slowly push the syringe plunger in with the index finger of your other hand. See Figure R.

- Keep the needle all the way into your skin until all of the medicine is injected under your skin and the insulin syringe is empty.



Figure R

Step 22. Release your pinched skin and pull the needle straight out. See Figure S.



Figure S

Step 23. Do not rub your injection area. A small amount of bleeding may happen.

If you have a small amount of bleeding, press a small clean, dry cotton pad over the area and press gently for 1 or 2 minutes, or until the bleeding has stopped. See Figure T.



Figure T

Disposing of used needles and syringes

- **Do not** reuse needles or syringes.
- Your healthcare provider will tell you how to throw away your used syringes and needles and other medical waste in an appropriate puncture-resistant disposal container such as a sharps (medical waste) container. See Figure U.

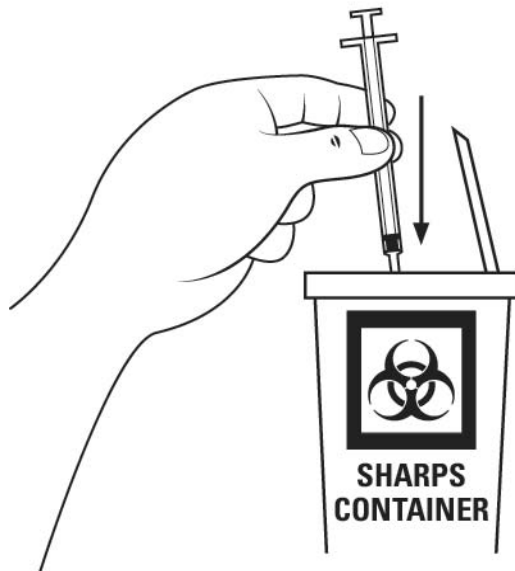


Figure U

- You may also contact your local health department for more information. There may be special state or local laws for properly

disposing of used needles, syringes, other medical waste, and sharps containers.

- **Do not** throw needles, syringes, or sharps containers in the household trash without first checking your state and local laws.
- **Do not** recycle the sharps container.
- Always keep your sharps container in a safe place and out of the reach of children.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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