Patient Authorization Form

SOMAVERT® (pegvisomant for injection)

This Patient Authorization Form authorizes your health care provider to disclose your health and personal information to US Bioservices, the administrator of the SOMAVERT Trial Prescription Program, and its employees, representatives, and agents (collectively, US Bioservices) in connection with the SOMAVERT Trial Prescription Program. In accordance with the Health Insurance Portability and Accountability Act of 1996 and related federal regulations and rules ("HIPAA").

Authorization.

I, _____ _____ _____ hereby authorize _____

First Middle Last Name Name of Physician "health care provider"

to disclose my individually identifiable health and medical information described below to US Bioservices solely for the authorized purposes described in this authorization form.

Description of Health and Medical Information That May Be Disclosed.

My health care provider may disclose individually identifiable health and other information that supports my participation in the SOMAVERT Trial Prescription Program. Information disclosed may include my name, address, date of birth, diagnosis/disease, treatment, financial information, medical records, and the specialty of my health care provider.

Authorized Purposes.

The authorized purposes are: (1) to evaluate my eligibility for inclusion in the SOMAVERT Trial Prescription Program and (2) if my participation in the program is approved, for the administration of the program to me, and (3) **if I choose to continue on SOMAVERT after the trial has concluded, my individually identifiable health and other information will be transferred to the Pfizer Bridge Program for reimbursement support and copay assistance. I understand the Pfizer Bridge Program may reach out to me and/or my physician for additional information.**

Expiration of Authorization.

My authorization shall expire (1) when my participation in the SOMAVERT Trial Prescription Program is not approved, or (2) at the conclusion of my participation in the SOMAVERT Trial Prescription Program, whichever is earlier.

Acknowledgments.

1. I understand that once my health care provider gives US Bioservices information about me based on this authorization, my medical and health information may be subject to disclosure and no longer protected by federal privacy regulations. I further understand and agree that US Bioservices may retain my medical and health information as disclosed under this authorization after this authorization expires for purposes related to the administration of the SOMAVERT Trial Prescription Program. I also understand that in the event of an audit, and only for purposes of such an audit, some information may also be disclosed to Pfizer (the manufacturer of SOMAVERT), even after this authorization has expired so long as the audit is for a period of time when this authorization was in effect.

2. I understand that I may refuse to sign this authorization form and that, unless allowed by law, my refusal to sign will not affect my ability to obtain treatment from my health care provider; or to seek payment or my eligibility for benefits. However, I understand that I may not be included in the SOMAVERT Trial Prescription Program if I refuse to sign this authorization form.

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3. I understand that I may revoke my authorization at any time by providing a written notice of same to my health care provider that refers to (or with a copy of) this authorization form. However, I understand that if I revoke this authorization, it will not affect prior disclosures made by my health care provider to US Bioservices in reliance of this authorization.

4. I understand and agree to the following:
Pfizer understands your personal and health information is private. The information you provide will only be used by Pfizer and parties acting on its behalf to send you the materials you requested and other helpful information and updates on SOMAVERT as well as related treatments, products, offers and services.

5. If you choose to continue on SOMAVERT after the trial has concluded you are consenting to the transferring of your information to the Pfizer Bridge Program for reimbursement support and copay assistance. The Pfizer Bridge Program may reach out to you and/or your physician for additional information.

☐ By checking this box, I also agree that Pfizer or companies acting on its behalf may send me materials about other health conditions, use my information to develop or improve products and services, or contact me in the future about health-related topics.

_____ _____
Signature of Patient or Patient's Personal Representative | Date

_____
Patient's Name (please print)

_____ _____
Name of Patient's Personal Representative (if applicable) | Relationship to Patient

Health care provider must give patient and/or patient's personal representative a signed copy of this form.
Health care provider received patient representative's authority on patient's behalf _____ (check)

Please see accompanying full Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOMAVERT safely and effectively. See full prescribing information for SOMAVERT.

SOMAVERT (pegvisomant) for injection, for subcutaneous use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

SOMAVERT is a growth hormone receptor antagonist indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery 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.(1)

----------DOSAGE AND ADMINISTRATION----------

- Administer a 40 mg loading dose subcutaneously under physician supervision (2.1)
- After proper injection instruction, on day after loading dose, patients or caregivers begin daily subcutaneous injections of 10 mg (2.1)
- Adjust dosage in 5 mg increments or decrements until serum IGF-I concentrations are maintained within age-adjusted normal range. Do not adjust dosage based on growth hormone (GH) levels or signs or symptoms of acromegaly (2.1)
- Dosage range is 10 to 30 mg once daily (2.1)
- Perform liver tests prior to first dosage and if greater than 3 time upper limit of normal should work-up prior to SOMAVERT administration (2.2)
- Follow reconstitution and injection procedures (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 10, 15, 20, 25 or 30 mg (as protein) lyophilized powder in single-use vial for reconstitution with supplied 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- *Hypoglycemia*: Monitor blood glucose in patients with diabetes mellitus and reduce anti-diabetic drug therapy as necessary (5.1)
- *Liver Test Elevations*: Should have more frequent liver tests and/or discontinue SOMAVERT (5.2)
- *Systemic Hypersensitivity*: Monitor closely when re-initiating SOMAVERT in patients with systemic hypersensitivity (5.5)

----------ADVERSE REACTIONS----------

Most common reported adverse reactions (> 6%) are infection, pain, nausea, diarrhea, abnormal liver tests, flu syndrome, injection site reaction (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (phone 1-800-438-1985 and www.pfizer.com) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Insulin and/or Oral hypoglycemic Agents:* Patients with acromegaly and with diabetes mellitus may require careful monitoring and dose reductions of insulin and/or oral hypoglycemic agents. (5.2, 7.1)
- *Opioids:* Patients on opioids may need higher SOMAVERT doses to achieve appropriate IGF-I suppression. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SOMAVERT is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended loading dose of SOMAVERT is 40 mg given subcutaneously, under healthcare provider supervision. Provide proper training in subcutaneous injection technique to patients or their caregivers so they can receive once daily subcutaneous injections. On the next day following the loading dose, instruct patients or their caregivers to begin daily subcutaneous injections of 10 mg of SOMAVERT.

Titrate the dosage to normalize serum IGF-I concentrations (serum IGF-I concentrations should be measured every four to six weeks). The dosage should not be based on growth hormone (GH) concentrations or signs and symptoms of acromegaly. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I concentrations would benefit from increased SOMAVERT dosage.

- Increase the dosage by 5 mg increments every 4-6 weeks if IGF-I concentrations are elevated.
- Decrease the dosage 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 Somavert dose given in multiple injections is converted to a single daily injection *[see CLINICAL PHARMACOLOGY (12)]*.

The recommended dosage range is between 10 to 30 mg given subcutaneously once daily and the maximum daily dosage is 30 mg given subcutaneously once daily.

2.2 Assess Liver Tests Prior to Initiation of SOMAVERT

Prior to the start of SOMAVERT, patients should have an assessment of baseline levels of liver tests [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP)]. For recommendations regarding initiation of SOMAVERT based on baseline liver tests and recommendations for monitoring of liver tests while on SOMAVERT, refer to Table 1 in *Warning and Precautions (5.2)*.

2.3 Loading Dose Injection Procedure

The following instructions are for the **healthcare provider** to reconstitute and prepare the 40 mg loading dose. The healthcare provider will need to reconstitute 2 vials of lyophilized powder of SOMAVERT each containing 20 mg of pegvisomant with supplied diluent [two vials of lyophilized powder and two 2.25 mL syringes containing diluent (Sterile Water for Injection) will be needed for the 40 mg loading dose]. The healthcare provider will also need to inject the reconstituted SOMAVERT solution twice into the patient's upper arm, upper thigh, abdomen, or buttocks (each injection in a different area).

(a) Before administering the loading dose, remove the first package (1 vial of lyophilized powder of SOMAVERT containing 20 mg of pegvisomant and one 2.25 mL syringe containing the diluent) from the refrigerator about 10 minutes prior to the planned injection time.

(b) Reconstitute the first 20 mg vial of lyophilized powder of SOMAVERT containing 20 mg of pegvisomant with diluent. When using the diluent in the 2.25 mL syringe, inject the contents of the syringe slowly onto the sides of the vial containing lyophilized powder of SOMAVERT. Do not inject the diluent directly on the powder.

(c) Do not invert the vial or shake the solution as this may cause denaturation of the pegvisomant protein. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution. If foaming of the reconstituted SOMAVERT solution is seen, the solution is likely damaged and therefore inappropriate to inject.

(d) Visually inspect the reconstituted SOMAVERT solution for particulate matter and discoloration prior to administration. The reconstituted solution should be clear. If the solution is cloudy, do not use it. Once reconstituted, the solution will contain 20 mg of pegvisomant in 1 mL of solution.

(e) Withdraw the 1 mL reconstituted SOMAVERT solution. The solution must be administered within 6 hours of reconstitution.

(f) Inject the first reconstituted SOMAVERT solution (20 mg/mL) subcutaneously into the patient's upper arm, upper thigh, abdomen, or buttocks using a 90-degree angle.

(g) Repeat steps (a) to (e) to reconstitute the second SOMAVERT dose of 20 mg.

(h) Finally, inject the second reconstituted SOMAVERT solution (20 mg/mL) subcutaneously into the patient's upper arm, upper thigh, abdomen, or buttocks using a 90-degree angle (different area than the first injection).

2.4 Maintenance Dose Injection Procedure

For patient or caregiver instructions for reconstitution and administration of daily doses (10 to 30 mg), see the Patient's Instructions for Use.

a) Before administering the dose, remove one package (1 vial of lyophilized powder of SOMAVERT containing 10, 15, 20, 25 or 30 mg of pegvisomant and one 2.25 mL syringe (containing the diluent) from the refrigerator about 10 minutes prior to the planned injection time.

b) Reconstitute the lyophilized powder of SOMAVERT with diluent. When using the diluent in the 2.25 mL syringe, inject the contents of the syringe slowly onto the sides of the vial containing lyophilized powder of SOMAVERT. Do not inject the diluent directly on the powder.

c) Do not invert the vial or shake the solution as this may cause denaturation of the pegvisomant protein. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution. If foaming of the reconstituted SOMAVERT solution is seen, the solution is likely damaged and therefore inappropriate to inject.

d) Visually inspect the reconstituted SOMAVERT solution for particulate matter and discoloration prior to administration. The reconstituted solution should be clear. If the solution is cloudy, do not use it. Once reconstituted, the solution will contain 10, 15, 20, 25 or 30 mg of pegvisomant in 1 mL of solution.

e) Withdraw the 1 mL reconstituted SOMAVERT solution. The solution must be administered within 6 hours of reconstitution.

f) Inject the reconstituted SOMAVERT solution subcutaneously into the upper arm, upper thigh, abdomen, or buttocks using a 90-degree angle.

3 DOSAGE FORMS AND STRENGTHS

For injection: 10, 15, 20, 25 or 30 mg (as protein) lyophilized powder in single-use vial for reconstitution with supplied 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia associated with GH lowering in patients with Diabetes Mellitus

GH opposes the effects of insulin on carbohydrate metabolism by decreasing insulin sensitivity; thus, glucose tolerance may improve in some patients treated with SOMAVERT. Patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary to avoid hypoglycemia in patients with diabetes mellitus.

5.2 Liver Test Elevations

Baseline serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TBIL), and alkaline phosphatase (ALP) levels should be obtained prior to initiating therapy with SOMAVERT. Table 1 lists recommendations regarding initiation of treatment with SOMAVERT, based on the results of these liver tests (LTs).

Asymptomatic, transient elevations in transaminases up to 15 times ULN have been observed in < 2% of subjects among two open-label trials (with a total of 147 patients). These reports were not associated with an increase in bilirubin. Transaminase elevations normalized with time, most often after suspending treatment (SOMAVERT should be used in accordance with the information presented in Table 2 with respect to liver test abnormalities while on Somavert treatment).

Table 1. Recommendations of Initiating SOMAVERT Based on Baseline LTs and Periodic Monitoring of LTs During SOMAVERT Treatment

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 bi-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 bi-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 2).

Table 2. Clinical Recommendations Based on Liver Test Results While on SOMAVERT

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). • 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 re-initiation 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.

5.3 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.

5.4 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).

5.5 Systemic Hypersensitivity

In subjects with systemic hypersensitivity reactions, caution and close monitoring should be exercised when re-initiating Somavert therapy *[see Adverse Reactions (6.3)]*.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other section of the labeling include:

- Hypoglycemia associated with GH lowering in patients with Diabetes Mellitus *[see Warnings and Precautions (5.1)]*
- Liver test elevations *[see Warnings and Precautions (5.2)]*
- Cross-reactivity with GH assay *[see Warnings and Precautions (5.3)]*
- Lipohypertrophy *[see Warnings and Precautions (5.4)]*
- Systemic hypersensitivity *[see Warnings and Precautions (5.5)]*

Elevations of serum concentrations of ALT and AST greater than ten times the ULN were reported in two patients (0.8%) exposed to SOMAVERT in pre-approval 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.

Elevations in ALT and AST levels were not associated with increased levels of TBIL and 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.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week randomized, placebo-controlled, double-blind, fixed-dose study of SOMAVERT in subjects with acromegaly, 32 subjects received placebo and 80 subjects received SOMAVERT once daily *[see Clinical Studies (14)]*. A total of 108 subjects (30 placebo, 78 Somavert) completed 12 weeks of study treatment.

Overall, eight patients with acromegaly (5.3%) withdrew from pre-marketing clinical studies because of adverse events, including two patients with marked transaminase elevations, one patient with lipohypertrophy at the injection sites, and one patient with substantial weight gain. Most adverse events did not appear to be dose-dependent. Table 3 shows the incidence of 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 3. Adverse Reactions in a 12-week Placebo-Controlled Study in Patients with Acromegaly*

	Placebo n=32	SOMAVERT		
		10 mg/day n=26	15 mg/day n=26	20 mg/day N=28
Infection†	2 (6%)	6 (23%)	0	0
Pain	2 (6%)	2 (8%)	1 (4%)	4 (14%)
Nausea	1 (3%)	0	2 (8%)	4 (14%)
Diarrhea	1 (3%)	1 (4%)	0	4 (14%)
Abnormal liver function tests	1 (3%)	3 (12%)	1 (4%)	1 (4%)
Flu syndrome	0	1 (4%)	3 (12%)	2 (7%)
Injection site reaction	0	2 (8%)	1 (4%)	3 (11%)
Dizziness	2 (6%)	2 (8%)	1 (4%)	1 (4%)
Accidental injury	1 (3%)	2 (8%)	1 (4%)	0
Back pain	1 (3%)	2 (8%)	0	1 (4%)
Sinusitis	1 (3%)	2 (8%)	0	1 (4%)
Chest pain	0	1 (4%)	2 (8%)	0
Peripheral edema	0	2 (8%)	0	1 (4%)
Hypertension	0	0	2 (8%)	0
Paresthesia	2 (6%)	0	0	2 (7%)

* 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).

6.2 Immunogenicity

In pre-marketing clinical studies, approximately 17% of the SOMAVERT-treated 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.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to SOMAVERT. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOMAVERT with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

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 always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Systemic hypersensitivity reactions including anaphylactic 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 Warnings and Precautions (5.5)]*.

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.

7 DRUG INTERACTIONS

7.1 Insulin and/or Oral hypoglycemic Agents

After initiation of SOMAVERT, patients with acromegaly and diabetes mellitus treated with insulin and/or oral hypoglycemic agents may require dose reductions of insulin and/or oral hypoglycemic agents *[see Warnings and Precautions (5.1)]*.

7.2 Opioids

In clinical studies, patients taking opioids often needed higher SOMAVERT doses to normalize IGF-I concentrations compared with patients not receiving opioids. The mechanism of this interaction is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. 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. Because animal reproduction studies are not always predictive of human responses, SOMAVERT should be used during pregnancy only if clearly needed.

8.3 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

SOMAVERT was not studied in patients with renal impairment and the safety and efficacy in these patients is not known.

10 OVERDOSAGE

In one reported incident of acute overdose with SOMAVERT during pre-marketing clinical studies, a patient self-administered 80 mg/day (2.7 times the maximum recommended maintenance dosage) for seven days. The patient experienced a slight increase in fatigue, had no other complaints, and demonstrated no significant clinical laboratory abnormalities.

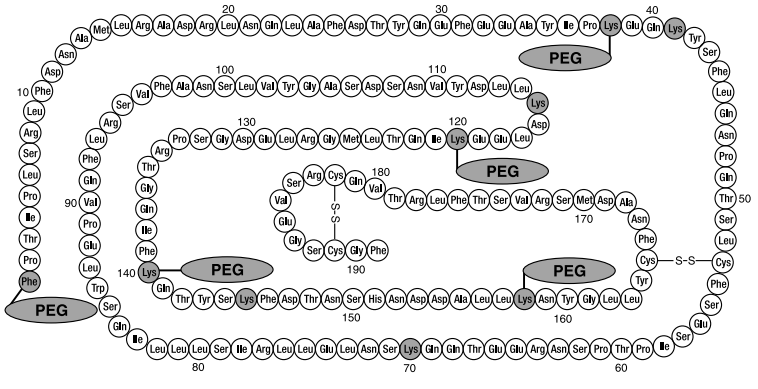
In cases of overdose, administration of SOMAVERT should be discontinued and not resumed until IGF-I levels return to within or above the normal range.

11 DESCRIPTION

SOMAVERT contains pegvisomant, 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. Binding of Somavert to the GH receptor results in disruption of the proper binding of the second GH receptor with inhibition of functional receptor dimerization and subsequent intracellular signaling.

Amino Acid Sequence of Pegvisomant Protein



Stippled residues indicate PEG attachment sites (Phe_1, Lys_{38}, Lys_{41}, Lys_{70}, Lys_{115}, Lys_{120}, Lys_{140}, Lys_{145}, Lys_{158})

Shown below are the amino acid substitutions in pegvisomant, relative to human GH.

hGH	Pegvisomant
His_{18}	Asp_{18}
Ala_{21}	Asn_{21}
Gly_{120}	Lys_{120}
Arg_{167}	Asn_{167}
Lys_{168}	Ala_{168}
Asp_{171}	Ser_{171}
Lys_{172}	Arg_{172}
Glu_{174}	Ser_{174}
Ile_{179}	Thr_{179}

SOMAVERT for injection is supplied as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of Sterile Water for Injection. SOMAVERT is available in single-dose sterile vials containing 10, 15, 20, 25 or 30 mg of pegvisomant protein (approximately 10, 15, 20, 25 and 30 U activity, respectively). Each vial 10, 15 and 20 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 mg of mannitol, 1.3 mg of sodium phosphate dibasic anhydrous, and 0.45 mg of sodium dihyrogen phosphate monohydrate. Each 30 mg vial also contains 2.04 mg of glycine, 54 mg of mannitol, 1.56 mg of sodium phosphate dibasic anhydrous, and 0.54 mg of sodium dihydrogen phosphate monohydrate.

SOMAVERT is supplied in packages that include a syringe with diluent (Sterile Water for Injection). 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.

12 CLINICAL PHARMACOLOGY

12.1 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 IGF-I, as well as other GH-responsive serum proteins such as free IGF-I, the acid-labile subunit of IGF-I (ALS), and insulin-like growth factor binding protein-3 (IGFBP-3).

12.2 Pharmacodynamics

Pegvisomant binds selectively to the GH receptor, and does not cross-react with 19 other cytokine receptors tested, including prolactin. Pegvisomant leads to decreased serum concentrations of IGF-I, free IGF-I, ALS, and IGFBP-3 *[see Clinical Studies (14, Figure 1)]*.

12.3 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 ± SEM serum pegvisomant concentrations after 12 weeks of therapy with daily doses of 10, 15, and 20 mg were 6600 ± 1330; 16,000 ± 2200; and 27,000 ± 3100 ng/mL, respectively.

The relative bioavailability of 1 x 30 mg pegvisomant was compared to 2 x 15 mg pegvisomant in a single dose study. The AUC_{inf} and C_{max} 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.

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 estimates ranging from 60 to 138 hours 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 Interaction Studies

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 Drug Interactions (7.2)]*.

Specific Populations

No pharmacokinetic studies have been conducted in patients with renal impairment, patients with hepatic impairment, geriatric patients, or pediatric patients and the effects of race on the pharmacokinetics of pegvisomant has not been studied. No gender effect on the pharmacokinetics of pegvisomant was found in a population pharmacokinetic analysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 20 mg 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.

Mutagenesis

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

Impairment of Fertility

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)

14 CLINICAL STUDIES

A total of one hundred twelve patients (63 men and 49 women) with acromegaly participated in a 12-week, randomized, double-blind, multi-center study comparing placebo and SOMAVERT. The mean ±SD age was 48±14 years, and the mean duration of acromegaly was 8±8 years. Ninety three had undergone previous pituitary surgery, of which 57 had also been treated with conventional radiation therapy. Six patients had undergone irradiation without surgery, nine had received only drug therapy, and four had received no previous therapy. At study start, the mean ± SD time since the subjects' last surgery and/or irradiation therapy, respectively, was 6.8 ± 0.93 years (n=63) and 5.6 ± 0.57 years (n=93).

Subjects were qualified for enrollment if their serum IGF-I, drawn after the required drug washout period, was ≥1.3 times the upper limit of the age-adjusted normal range. They were randomly assigned at the baseline visit to one of four treatment groups: placebo (n=32), 10 mg/day (n=26), 15 mg/day (n= 26), or 20 mg/day (n=28) of SOMAVERT subcutaneously IGF-I. The primary efficacy endpoint was IGF-I percent change in IGF-I concentrations from baseline to week 12. The three groups that received SOMAVERT showed statistically significant ($p<0.01$) reductions in serum levels of IGF-I compared with the placebo group (Table 4).

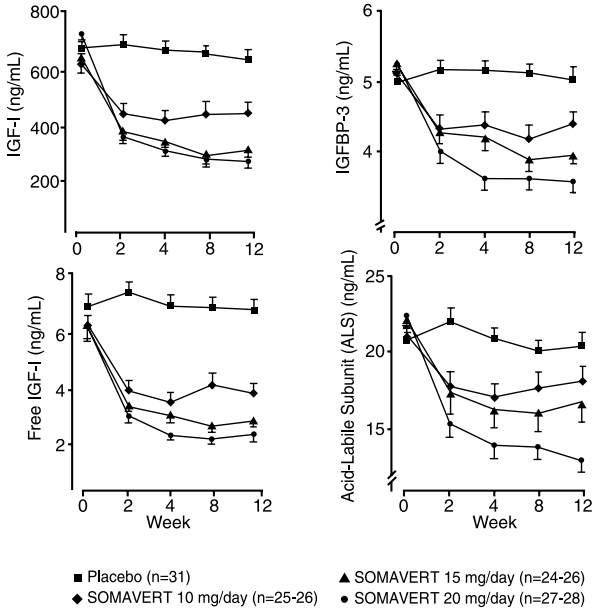
Table 4. Mean Percent Change from Baseline in IGF-I at Week 12 for Intent-to-Treat Population

	Placebo n=31	SOMAVERT		
		10 mg/day n=26	15 mg/day n=26	20 mg/day n=28
Mean baseline IGF-I (ng/ml) (SD)	**670 (288)**	**627 (251)**	**649 (293)**	**732 (205)**
Mean percent change from baseline in IGF-I (SD)	**-4.0 (17)**	**-27 (28)**	**-48 (26)**	**-63 (21)**
SOMAVERT minus Placebo (95% CI for treatment difference)		**-23* (-35, -11)**	**-44* (-56, -33)**	**-59* (-68, -49)**

* $P<0.01$; n = number of patients; SD = standard deviation

There were also reductions in serum levels of free IGF-I, IGFBP-3, and ALS compared with placebo at all post-baseline visits (Figure 1).

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



After 12 weeks of treatment, the following percentages of patients had normalized IGF-1 (Figure 2):

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

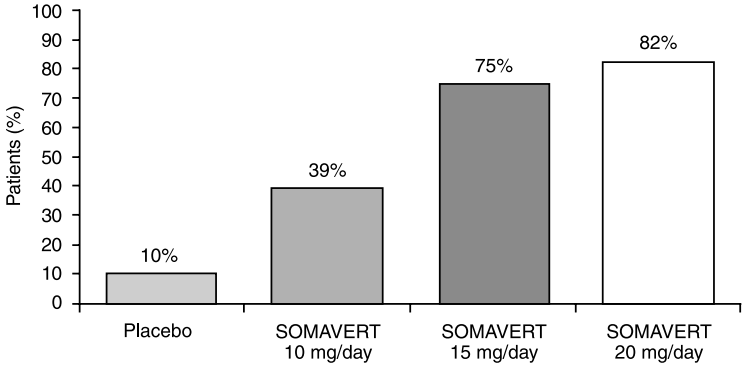


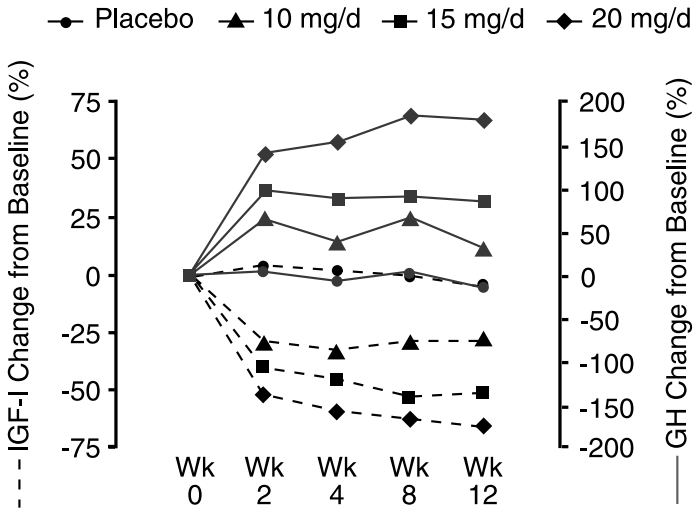
Table 5 shows the effect of treatment with SOMAVERT on ring size (standard jeweler's sizes converted to a numeric score ranging from 1 to 63), and on signs and symptoms of acromegaly. Each individual score for a sign or symptom of acromegaly (for soft-tissue swelling, arthralgia, headache, perspiration and fatigue) was based on a nine-point ordinal rating scale (0 = absent and 8 = severe and incapacitating), and the total score for signs or symptoms of acromegaly 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 5. Mean Change from Baseline (SD) at Week 12 for Ring Size and Signs and Symptoms of Acromegaly

	Placebo n=30	SOMAVERT		
		10 mg/day n=26	15 mg/day n=24-25	20 mg/day n=26-27
Ring size	-0.1 (2.3)	-0.8 (1.6)	-1.9 (2.0)	-2.5 (3.3)
Total score for signs and symptoms of acromegaly	1.3 (6.0)	-2.5 (4.3)	-4.4 (5.9)	-4.7 (4.7)
Soft-tissue swelling	0.3 (2.3)	-0.7 (1.6)	-1.2 (2.3)	-1.3 (1.3)
Arthralgia	0.1 (1.8)	-0.3 (1.8)	-0.5 (2.5)	-0.4 (2.1)
Headache	0.1 (1.7)	-0.4 (1.6)	-0.3 (1.4)	-0.3 (2.0)
Perspiration	0.1 (1.7)	-0.6 (1.6)	-1.1 (1.3)	-1.7 (1.6)
Fatigue	0.7 (1.5)	-0.5 (1.4)	-1.3 (1.7)	-1.0 (1.6)

Serum growth hormone (GH) concentrations, as measured by research assays using antibodies that do not cross-react with pegvisomant, rose within two weeks of beginning treatment with SOMAVERT. The largest increase in GH concentration was seen in patients treated with doses of SOMAVERT 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, the rise in GH was inversely proportional to the fall in IGF-I and generally stabilized by week 2. Serum GH concentrations remained stable in patients treated with SOMAVERT for the average of 43 weeks (range, 0-82 weeks).

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



In the open-label extension to the clinical study, 109 subjects (including 6 new patients) with mean treatment exposure of 42.6 weeks (range 1 day – 82 weeks), 93 (85.3%) subjects had an adverse event, 16 (14.7%) had an SAE, and 4 (3.7%) discontinued due to an AE (headaches, elevated liver function tests, pancreatic cancer, and weight gain). A total of 100 (92.6%) of the 108 subjects with available IGF-I data had a normal IGF-I concentration at any visit during the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

SOMAVERT (pegvisomant) is supplied in the following strengths and package configurations:

SOMAVERT (pegvisomant) syringe for injection	
Package Configuration	**NDC**
Single 10 mg dose vial with 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle	0009-7166-01
Single 15 mg dose vial with 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle	0009-7168-01
Single 20 mg dose vial with 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle	0009-7188-01
Single 25 mg dose vial with 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle	0009-7199-01
Single 30 mg dose vial with 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle	0009-7200-01

Storage

Prior to reconstitution, SOMAVERT should be stored in a refrigerator at 2 to 8ºC (36 to 46ºF). Do not freeze.

17 PATIENT COUNSELING INFORMATION

See FDA- approved patient labeling (Patient Information and Instructions for Use).

Inform patients (and/or their caregivers) of the following information to aid in the safe and effective use of SOMAVERT:

- Not to use SOMAVERT if they are allergic to SOMAVERT or anything in it.
- They will need blood testing to check IGF-I levels and liver tests before and during treatment with SOMAVERT and that the dose of SOMAVERT may be changed based on the results of these tests
- SOMAVERT has not been studied in pregnant women and instruct them to notify their healthcare provider as soon as they are aware that they are pregnant.
- It is not known whether SOMAVERT is excreted in human milk and instruct them to notify their healthcare provider if they plan to do so.

Advise patients (and/or their caregivers) of the following adverse reactions:

- The most common reported adverse reactions are injection site reaction, elevations of liver tests, pain, nausea, and diarrhea.
- If they have liver test elevations they may need to have more frequent liver tests and/or discontinue SOMAVERT. Instruct patients to immediately discontinue therapy and contact their physician if they become jaundiced.
- GH-secreting tumors may enlarge in people with acromegaly and that these tumors need to be watched carefully and monitored by MRI imaging.
- Thickening under the skin may occur at the injection site that could lead to lumps and that switching sites may prevent or lessen this.
- If they have diabetes mellitus, they may require careful monitoring and dose reductions of insulin and/or oral hypoglycemic agents while on SOMAVERT.
- If they take opioids, they may need higher SOMAVERT doses to achieve appropriate IGF-I suppression.

Advise patients that SOMAVERT is supplied as lyophilized powder in different strengths of 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg in a sterile glass vial within a package with a 2.25 mL syringe containing 1 mL of diluent (Sterile Water for Injection) and a separate 27 gauge ½ inch safety needle. Advise patients that the vial stoppers are not made with natural rubber latex. Advise patients to follow the directions for reconstitution provided with each package. Include that spraying the diluent directly onto the powder may cause foaming and that shaking may induce denaturation (destruction) of the active ingredient (therefore **do not shake**).

Advise patients that the package of SOMAVERT should be stored in a refrigerator 2 to 8ºC (36 to 46ºF) prior to use. It should NOT BE FROZEN.

Distributed by

Pfizer **Pharmacia & Upjohn Co**

Division of Pfizer Inc, NY, NY 10017

LAB-0782-1.0

PATIENT INFORMATION
SOMAVERT® (SOM-ah-vert)
(pegvisomant)
for injection, for subcutaneous use

What is SOMAVERT?

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

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

Before using SOMAVERT, tell your healthcare provider about all your medical conditions, including if you:

- are allergic to pegvisomant or any of the ingredients in SOMAVERT. See the end of this leaflet for a complete list of ingredients in SOMAVERT.
- 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. Tell your healthcare provider if you become pregnant while using SOMAVERT.
- 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 over-the-counter 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). Your healthcare provider may change your dose of SOMAVERT if you take opioids.

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

How should I use SOMAVERT?

- Read the **Instructions for Use** at the end of this Patient Information for information about the right way to use SOMAVERT.
- Your healthcare provider should do blood tests to check your liver and insulin-like growth factor-I (IGF-I) levels before you start and while you use SOMAVERT. Your healthcare provider may need to change your dose of SOMAVERT.
- SOMAVERT is given 1 time each day as an injection under your skin (subcutaneous). Some people may need to give 2 injections for their dose each day. Your healthcare provider will tell you if you need to give 2 injections for your dose.
- Your first injection of SOMAVERT should be given by your healthcare provider.
- Your healthcare provider will teach you or your caregiver how to use SOMAVERT.
- If you use 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.

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.
- **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
- **skin thickening at your injection site that could lead to lumps (lipohypertrophy)**
- **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
- nausea
- flu syndrome
- injection site reaction
- diarrhea
- abnormal liver tests. If your liver test results are too high you may have to have more frequent liver tests.

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

Call your doctor 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.

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. You can ask your pharmacist or healthcare provider for information about SOMAVERT that is written for health professionals.

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

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

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

Revised: April 2016

LAB Number: 0783-1.0

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

Read these Instructions for Use before you start using SOMAVERT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment. Your healthcare provider should show you or a caregiver how to inject SOMAVERT the right way before you inject it for the first time.

Important:

- **Do not share your SOMAVERT syringes or needles with other people. You may give other people a serious infection, or get an infection from them.**
- SOMAVERT comes in a vial as a white block of powder. You must mix SOMAVERT with a liquid (diluent) before you can use it. The liquid comes in a single-dose pre-filled syringe labeled 'Sterile Water for Injection'. **Do not** use any other liquid to mix with SOMAVERT.
- **You must use 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.

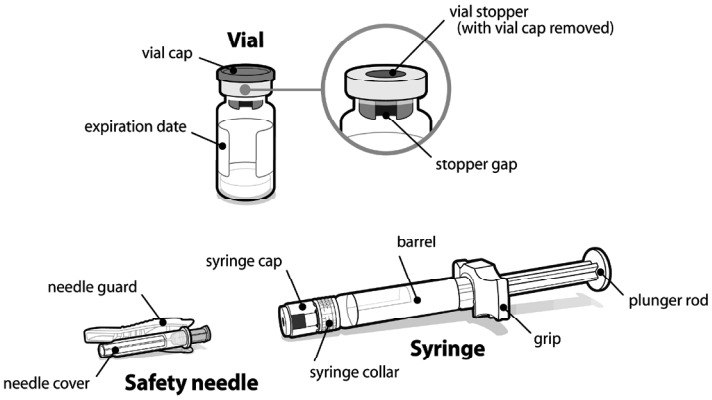
Step 1. Things you need

A single SOMAVERT pack containing:

- A vial of SOMAVERT powder.
- A pre-filled syringe.
- A safety needle.

You will also need:

- A cotton ball.
- An alcohol swab.
- A sharps disposal container. **See "Dispose" at the end of these instructions.**

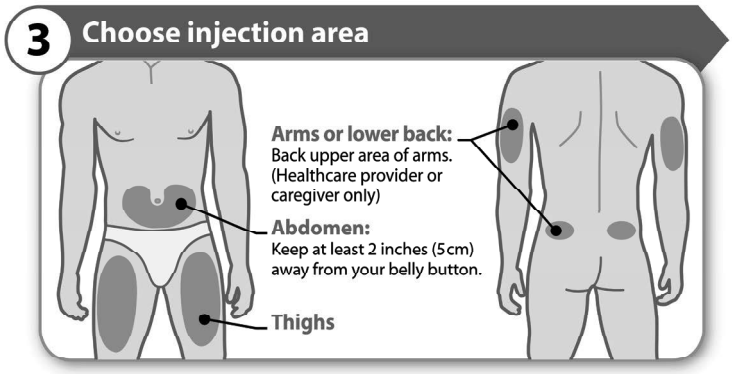


Step 2. Getting ready

Before you start:

- Only mix SOMAVERT and the liquid when you are ready to inject your dose.
- Remove a single SOMAVERT pack from the refrigerator and allow it to come to room temperature in a safe place at least **10 minutes** before you need to use it.
- **Do not** heat the SOMAVERT pack by using a heat source such as hot water or microwave. Let it warm up on its own.
- Wash your hands with soap and water, and dry completely.
- 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)

Step 3. Choose injection area



- Choose a different location within an area for each injection.
- Avoid bony areas or areas that are bruised, red, sore or hard, or areas that have scars or skin conditions.
- Clean the injection area with the alcohol swab as instructed by your healthcare provider.
- Allow the injection area to dry.

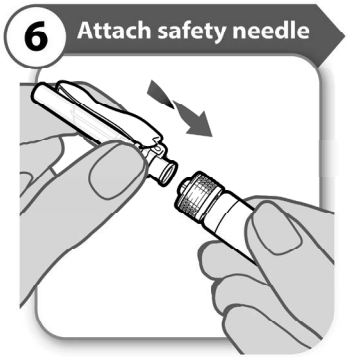
Step 4. Remove vial cap

- Remove the cap from the vial.
- Throw the cap away. It is not needed again.
  Caution: Do not let anything touch the vial stopper.

Step 5. Remove syringe cap

- Snap off the syringe cap leaving the syringe collar in place. 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.

Step 6. Attach safety needle

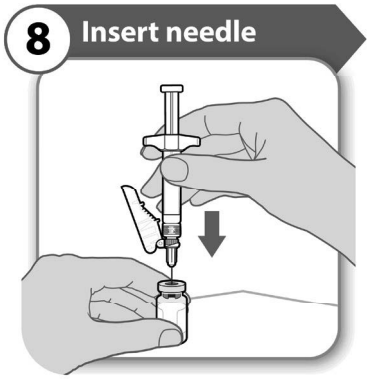


- Push down and twist the safety needle firmly onto the syringe as far as it will go.

Step 7. Remove needle cover

- 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.

Step 8. Insert needle



- 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.

Step 9. Add liquid

- 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. This creates foam. Foam makes the medicine unusable.
- **Do not withdraw the needle yet.**

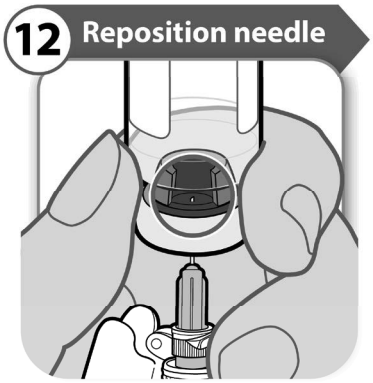
Step 10. Swirl vial

- Support both the syringe and vial in 1 hand, as shown.
- Gently and **slowly** 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.
  Do not shake.

Step 11. Check medicine

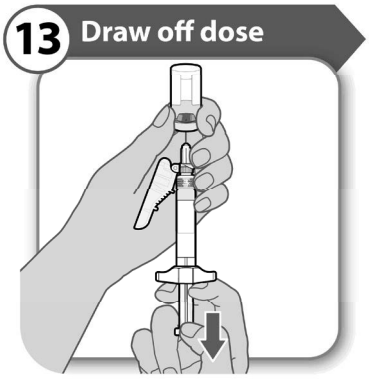
- Keeping the needle in the vial, look carefully at the medicine. It must be clear and free of particles.
- **Do not** use if:
  - the medicine is cloudy or hazy
  - the medicine has any color at all
  - there are any particles or foam in the vial
- If you have any doubts about your medication go to www.SOMAVERT.com or call 1-800-645-1280.

Step 12. Reposition needle



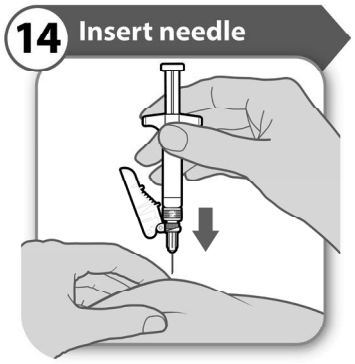
- Turn the vial so that you can see the stopper gap, as shown.
- Pull the needle down so that the needle tip is at the lowest point in the liquid. This will help you to draw off as much liquid as possible.
- Check that the plunger rod has not moved. If the plunger rod has moved, then push it back all the way into the syringe. This ensures that all air is removed from the syringe before you draw off the dose.

Step 13. Draw off dose



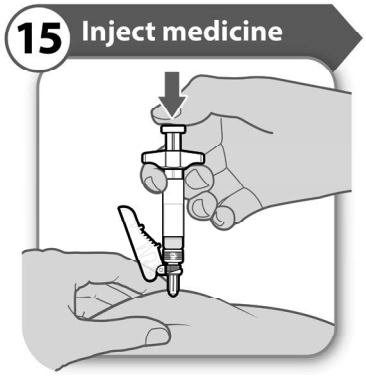
- Slowly pull back the plunger rod to withdraw as much medicine as possible from the vial.
  Note: If you see air in the syringe, tap the barrel to float the bubbles to the top, and then gently push the bubbles out **into the vial**.
- Pull the needle out of the vial.

Step 14. Insert needle



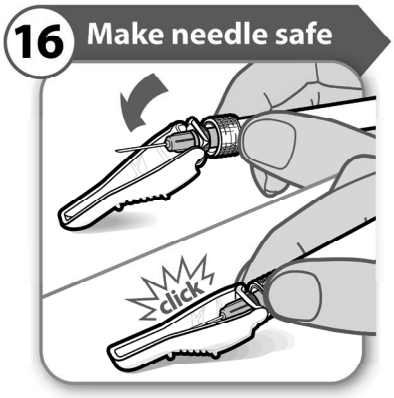
- Gently pinch the skin at the site of injection.
- Insert the needle to its full depth into the pinched skin.

Step 15. Inject medicine



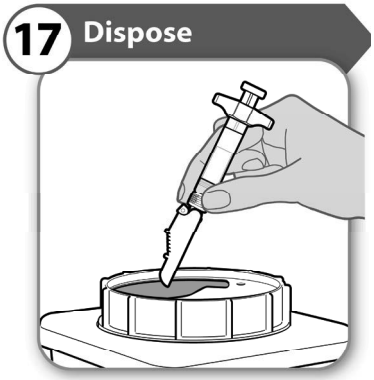
- Push the plunger rod down slowly until the barrel is empty.
  Note: Make sure you keep the needle in at full depth.
- Release the pinched skin and pull the needle straight out.

Step 16. Make needle safe



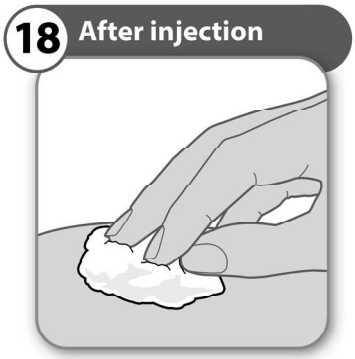
- Fold the needle guard over the needle.
  Gently apply pressure using a hard surface to lock the needle guard in place.
- Note: You will hear a click when the needle guard has been locked.

Step 17. Dispose



- Put your used syringes in a FDA cleared sharps disposal container right away after use.
- Do not throw away (dispose of) syringes in your household trash.
  Note: If you do not have a FDA cleared sharps disposal container, please refer to the safe syringe disposal information on the right hand side of this leaflet.

Step 18. After injection



- If necessary, use a clean cotton ball and press lightly on the injection area.
- **Do not rub the area.**

QUESTIONS AND ANSWERS

What should I do if anything has accidentally touched the vial stopper?

- Clean the vial stopper with a fresh alcohol wipe, and leave it to dry completely. If you are unable to clean the stopper, do not use the vial.

What should I do with the syringe if it has been dropped?

- Do not use it even if it looks undamaged. Dispose of the syringe in the same way as a used syringe. You will need a replacement syringe.

How many times can I safely insert the needle into the vial stopper?

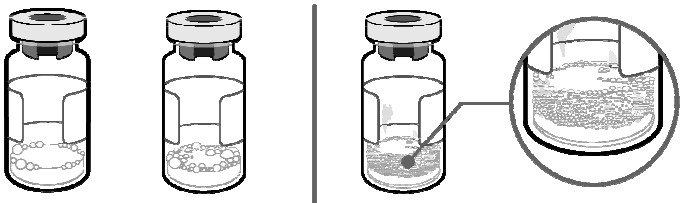
- Only 1 time. Withdrawing and reinserting greatly increases the risk of needle damage, and will blunt the needle. This can cause discomfort and increases risk of skin damage and infection. There is also a risk you may lose some of the medicine.

Is it okay to shake the vial if the powder is not dissolving?

- No. Never shake the vial. Shaking can destroy the medicine and create foam. The powder may take a few minutes to dissolve fully, so continue swirling the vial gently until the liquid is completely clear.

How can I tell if there is any foam in the vial?

- Foam looks like a mass of small bubbles that float as a layer to the top of the liquid. Do not inject SOMAVERT if it has foamed.



Tiny air bubbles are acceptable

A layer of foam is **not** acceptable

How can I prevent the medicine from foaming?

- Press the plunger very slowly so that the liquid gently runs down the inside of the vial. Do not spray the liquid directly onto the powder, because this creates foam. This will also reduce the swirling time and allow more of the medicine to be drawn off.

I can see some air in the syringe. Is this okay?

- Tiny air bubbles in the liquid are normal and are safe to inject. However, it is possible to accidently draw air into the syringe, which should be removed before injecting. Bubbles or air gaps that float to the top of the liquid should be pushed back out into the vial.

Why can I not get all of the medicine out of the vial?

- The shape of the vial means that a very small amount of the medicine will be left behind in the vial. This is normal. To ensure that only a trace of medicine remains, make sure the needle tip is as low as it can be in the vial when drawing off your dose.

What should I do if I have any doubts about my medicine?

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

Safe syringe disposal information

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use, leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

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

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